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OCT 12 1944

BRITISH MEDICAL JOURNAL

JOURNAL OF THE BRITISH MEDICAL ASSOCIATION

SATURDAY SEPTEMBER 23 1944

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BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 23 1944

INFLUENCE OF SYNTHETIC OESTROGENS UPON ADVANCED MALIGNANT DISEASE

BY

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WITH AN

ADDENDUM by P. C. KOLLER, D.Sc., Ph.D.

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In an investigation of the mechanism of action of tumour-producing compounds it was found that many carcinogenic hydrocarbons possess the property of retarding the growth of tissues, both normal and malignant (Haddow, 1935; for later references see Badger, Elson, Haddow, Hewett, and Robinson, 1942). In these compounds the correlation between carcinogenicity and growth-inhibitory activity assumes considerable statistical significance, and it was further suggested that it is of aetiological importance as well, tumour production by these substances being envisaged as a cellular adaptation to a protracted period of growth repression. In subsequent work to elucidate the molecular conditions determining inhibitory action, attention was paid to the synthetic oestrogens. It may be recalled that a few of the carcinogenic hydrocarbons themselves possess slight oestrogenic activity, while in certain cases these two classes show interesting relationships on chemical grounds. Thus the results obtained in animal experiments with a number of derivatives of the oestrogen triphenylethylene (which may be likened, for instance, to a 9-phenylphenanthrene with one ring disrupted) indicated that growth-inhibitory activity may still be shown by compounds which depart from the polycyclic structure and possess only a resemblance in their carbon skeleton.

These findings may possibly be correlated with the fact that, contrariwise, certain of the oestrogens exert carcinogenic action in animals, although in a somewhat restricted sense and in experimental circumstances (of dosage, strain susceptibility, etc.) which are unlikely to be duplicated under the conditions of medication in the human subject. The reviews of Gardner (1939) and Allen (1942) cite numerous instances of tumours occurring in experimental animals after long-continued treatment with oestrogens, examples being carcinoma of the cervix uteri in mice, uterine fibromyomas in guinea-pigs, mammary cancer, interstitial-cell tumours of the testis in mice, pituitary adenomatosis in mice and rats, tumours of the suprarenal cortex in mice, osteogenic transformations in mice, and various lymphoid and connective-tissue tumours, including sarcoma. The induction of animal tumours by oestrogens is most readily elicited, although by no means exclusively, in those tissues which are highly responsive to the physiological action of such compounds, and the greatest number of reports deal with the production of mammary cancer in mice—e.g., by the synthetic oestrogens stilboestrol (Lacassagne, 1938; Shimkin and Grady, 1940) and triphenylethylene (Robson and Bonser, 1938). Since the testis is markedly sensitive to oestrogen action, which results in varying degrees of atrophy, the production of hypertrophy and tumours of the interstitial cells in the testes of mice receiving oestrogens is of especial significance (e.g., Gardner, 1937; Hooker, Gardner, and Pfeiffer, 1940; Bonser and Robson, 1940). There is, in short, a group of growth-inhibitory substances which are clearly associated with the production of individual classes of tumour in laboratory animals under specially defined experimental conditions. The oestrogens thus provide a further example of the relation (only apparently paradoxical) that compounds possessing growth-retarding properties in certain circumstances may also have either with the physiological stimulation of growth or with the induction of tumours.

The growth-retarding property of polycyclic aromatic compounds, although under some experimental conditions more marked than that shown by the oestrogens, remains a subject for persistent investigation rather than clinical application. However, it was judged reasonable to undertake the clinical trial of synthetic oestrogens in advanced human cancer which was beyond treatment by either surgery or radiation, with particular reference to tumours arising from such normal tissues as are most reactive to the physiological stimulus of these compounds—e.g., tumours of the breast or of the testis. Such an investigation is facilitated by the ready availability and low toxicity of the synthetic oestrogens.

The present paper reports the findings in 40 cases of carcinoma of the breast and in 33 cases of malignant disease in other organs, the majority of which were treated with triphenylchlorethylene, and the first of which (carcinoma of the bladder —see below) began treatment on Feb. 18, 1941. Triphenylchlorethylene is of interest in two respects: first, because of its comparatively prolonged action (cf. Robson, Schönberg, and Fahim, 1938), which seems to be related to its insolubility in body fluids; and, secondly, since Emmens (1941) showed it to be a true oestrogen—that is, one acting directly, or after chemical changes which can be effected locally, in contrast with the pro-oestrogens (including the parent hydrocarbon triphenylethylene), which require to pass into the general circulation before exhibiting oestrogenic properties. Apart from those cases treated with triphenylchlorethylene, 7 were treated with the compound in which the chlorine atom is replaced by a methyl group (triphenylmethylethylene), and 14 with stilboestrol.

A. Triphenylchlorethylene

1. Late Malignant Disease of the Breast

Table I summarizes the data obtained in 22 cases. The drug was administered by mouth in all save Nos. 21 and 22, which received it by the intramuscular injection of an aqueous dispersion.

It is clear that a proportion of cases showed a significant —although temporary—retardation of the growth of the tumour. Indeed, an initial regression of the lesions occurred in 10 of the 22 cases (Nos. 1, 2, 4, 6, 7, 12, 17, 18, 20, 21, Table I). In Case 1 a skin nodule remained stationary for a period of three months, during which the primary tumour was regressing. Again, secondary deposits in the lung developed in Case 18 during treatment, although the lesion in the breast showed all of whom are now dead or have steadily advancing lesions. It may be noted that the degree of retardation obtained was probably much less than could be expected from local palliative *x*-irradiation.

In responsive cases the sequence of changes has been characteristic, consisting of a purplish discoloration of lesions previously red, a flattening followed by disappearance of small skin nodules, and the ulceration and disappearance of larger

TABLE I.—*22 Cases of Late Malignant Disease of the Breast treated with Triphenylchlorethylene*

Case	Age (yrs.)	Previous History	Condition at Beginning of Treatment (No biopsy or section unless stated)	Treatment (Amounts in Grammes refer to Triphenylchlorethylene)	Result of Treatment (b.t. = Beginning of treatment)
1	71	Lump breast for 1 yr., ulcerated	Ulcer 12 × 9 cm. replacing breast. Nodule over sternum. Enlarged lymph nodes both axillae	10 g. per week initial. 252 g. in 3 m. Interval of 2 m.; then 336 g. in 8 m.	Almost complete regression of tumour within 3 m., then steady growth. No regression of nodule or of axillary nodes. Died of lesion and metastases 16 m. after b.t.
2	33	Lump under arm 18 m. *X*-ray therapy. Recurrence 1 yr. later	Pregnant. Tumour lt. breast. Skin nodules; nodes involved	21 g. per week for 2 m. Interval of 2 m. while patient confined; then 525 g. in 6½ m.	Entire diseased breast sloughed off 4 m. after b.t. Fresh nodules in opp. breast. Death 10 m. after b.t.
3	71	Retraction and ulc. lt. nipple for 5 yrs.	Lt. nipple destroyed by ulc. Small tumour beneath nipple. Fixed supraclav. and axillary nodes	21 g. per week for 9 m. Total 756 g.	Stationary over 13 m. Death (cardiac condition) 13 m. after b.t.
4	40	Radical amp. lt. breast 2 yrs. ago, then *x*-ray therapy. *X*-ray therapy for recurrent nodule 8 m. ago	Extensive lesions thorax both sides. Nodes rt. axilla and rt. side neck	21 g. per week for 8 m. Total, 672 g.	Slight diminution in lesions. Treatment stopped; nausea and vertigo
5	53	Lump rt. breast 4 yrs. Local mastectomy and post.-op. *x*-ray therapy	Menopausal. Recurrence mastectomy area, 11 × 16 cm. Rt. supraclavicular nodes. Metas. rt. lung	21 g. per wk. for 3 m. Total, 252 g.	No alteration in recurrence. Growth of lung metastases. Died 14 m. after b.t.
6	48	Radical amp. 9 yrs. ago. Nodules in scar 1 yr. ago	Skin recurrence 13 cm. diam. Hard supraclavicular node. Spheroidal-cell carc.	21 g. per week for 18 m.	Within 5 m. ulc. nodules epithelized. Fresh nodules peripherally. Metas. in vertebrae and regional nodes during treatment
7	63	Lump rt. breast; *x*-ray therapy, then radical amp.	Multiple nodules chest wall; hard supraclavicular nodes. Spheroidal-cell carc.	14–21 g. per week for 15 m. Total, 980 g.	After 10 days regression marked. In 3 m. all lesions disappeared. In further 3 m. recurrence, although treatment maintained. Metas. locally and in lungs. Death 17 m. after b.t.
8	55	Lump rt. breast 1931, tr. radium 1932; recurrence 1942	Recurrence over sternum 5 cm. diam. Lt. supraclav. node	31·5 g. weekly. Total 756 g. in 6 m.	Extension of disease. Died 11 m. after b.t.
9	48	Amp. r. breast Jan., 1941; *x*-ray therapy Oct., 1941, to skin nodules. Disease advancing	Intradermal carc. chest wall. Nodes axillae and supraclavicular regions. Scirrhous cart.	21 g. per week. Total, 279 g. in 2 m.	Died, local extension and metas., 5 m. after b.t.
10	63	Lump rt. breast, ulc., 1939. *X*-ray therapy palliative, poor response	Ulc. tumour breast, fixed axillary nodes. Spheroidal-cell carc.	21 g. per week. Total, 588 g. in 7 m.	No change during treatment
11	60	Lump lt. breast, uncertain duration. Ulc. 1941	Ulc. tumour. Hard supraclav. and axillary nodes. Spheroidal-cell carc.	21 g. per week. Total, 420 g. in 5 m.	No regression. Died 6 m. after b.t.
12	52	Lump rt. breast and both axillae. *X*-ray therapy, incomplete resolution, July, 1941	Post-menopausal. Large mass rt. breast and axillae. Extensive skin involvement	21 g. per week. Total, 420 g. in 5 m.	Possibly slight local improvement. Lung metas. developed. Died 8 m. after b.t.
13	53	Recurrent nodules after radical amp. lt. breast	Nodules lt. chest wall, axilla, and supraclav. region. Scirrhous carc.	18 g. per week. Total, 429 g. in 6 m.	No regression. Not followed after 6 m.
14	65	Radical mastectomy, then *x*-ray therapy, 1941	Recurrence in scar; deposits lt. axilla and both supraclav. regions	21 g. per week. Total, 336 g. in 5 m.	No regression. Alive, but lesions advancing
15	49	Radical mastectomy, 1936. *X*-ray therapy to recurrence. Temp. improvement	Recurrent carc. lt. supraclav. and axillary nodes. ? Metas. dorsal vertebrae. Scirrhous carc.	21 g. per week for 3 m. Total uncertain	No regression. Alive but deteriorating
16	39	Recurrent carc. lt. breast. Radium and *x*-ray therapy	Large mass lt. breast and rt. axilla. Scirrhous carc.	21 g. per week. Total, 630 g. in 7 m.	After stopping treatment, severe menorrhagia. Lesions stationary; total observation 18 m.
17	54 (male)	Radical amp. lt. breast, 1939. *X*-ray palliative therapy local recurrence	Two nodules in op. scar lt. chest. ? Metas. lt. femur and ischium	21 g. per week. Total, 228 g. in 3 m.	Disappearance of nodules after b.t.; recurrence in next 6 m. Metas. in sacrum. Died 11 m. after b.t.
18	65	Lump rt. breast 2 yrs. Ulc. 1 yr.	Ulc. mass 11 × 13 cm. Nodes supraclav. region and both axillae. Spheroidal-cell carc.	21 g. per week. Total, 189 g. in 9 weeks	Mass reduced to 9 × 10 cm. Lung metas. developed during treatment
19	52	Lump lt. breast	Mass filling whole lt. breast. Large ulc. area; nodules lt. chest wall; nodes axilla and supraclav. region. Scirrhous carc.	21 g. per week. Total, 250 g. in 4 m.	Lesion advanced during treatment
20	56	Ulc. lump rt. breast; recurrence after *x*-ray therapy	Tumour 10 × 9 cm. whole rt. breast; ulcerated. Nodes rt. pectoral region	21 g. per week. Total, 1,000 g. in 9 m.	Tumour shrank to 6 × 5 cm. Ulcer smaller but not healed. 7 m. after b.t. ulcer enlarging, and 11 m. after, tumour enlarging, then slow advance. Slight vaginal bleeding and nausea
21	63	Radical amp. for carc. lt. breast, 1932. Recurrence over sternum	Ulc. mass 7 × 4 cm., 4–5 cm. deep. Spheroidal-cell carc.	15 c.cm. dispersion of triphenylchlorethylene by injection in 5 m.	Lesion much flattened, area unaltered. Fresh cervical metas. 4 m. after b.t., then palliative *x*-ray therapy. Nausea during treatment
22	63	Lt. breast "shrinking" for 2 yrs.	Whole lt. breast involved. Nodes lt. supraclavicular area. Lung metas.	9 c.cm. dispersion of triphenylchlorethylene by injection in 3 m.	Lesions progressed. Died 6 m. after treatment stopped

regression. No evidence was obtained to suggest that the drug will prevent the development of metastases. On the contrary, the impression was gained that the malignant cells become in time progressively more resistant to the inhibitory effects produced by the drug at an earlier stage. Thus only one of the cases has shown prolonged arrest, and the ultimate course of the disease has been in no way altered in the remaining patients, nodules and masses, followed by epithelization of the area. In exceptional cases the degree of response was considerable. One of these (Case 1) is illustrated in Fig. 1.

Biopsy material was examined in 4 of the cases showing regression of the primary tumour. All were highly cellular types, as were also 2 of the 3 cases which maintained a stationary condition, the remaining case being of scirrhous type.

Hence there would seem to be a greater sensitivity to the action of the oestrogen in highly cellular than in scirrhous carcinomata. In one case (No. 18, spheroidal-cell carcinoma) serial biopsy during treatment revealed the disappearance of mitoses, and a diminution in the staining affinities of the cells: the appearances did not resemble those seen after *x*-irradiation. The cellular changes in this case are shown in Fig. 2. Case 17, in which a marked response was obtained, is of special interest as being the only male in the series.

The secondary signs of drug action included nausea, pigmentation of the mammary areola, uterine bleeding, improved appetite, and gain in weight. One or more of these changes occurred with special frequency in the group of cases showing some degree of regression. Relief of pain seemed a real finding in 4 cases—Nos. 6, 10, 17, 21.

2. Miscellaneous Cases

This series consisted of 30 cases of advanced malignant disease other than carcinoma of the breast. They comprised carcinomata of the skin, maxillary antrum, urinary bladder, ovary, rectum, and testis, with reticulo-endothelial growths, and one example each of chronic myeloid leukaemia and chronic lymphatic leukaemia. The period of treatment varied between 1 and 16 months. In nearly every case the drug seemed to have no effect on the course of the disease, although side-effects occurred in some. In other cases treatment was

TABLE II.—*14 Cases treated with Stilboestrol*

Case	Age	Previous History	Condition at Beginning of Treatment	Date Treatment Started	Dosage of Stilboestrol	Result of Treatment
1	42	Rt. radical mastectomy, 1939. H.V. therapy to recurrence Dec., 1941–Sept., 1942. Further recurrence Dec., 1942	General condition good. Multiple skin nodules scar area. Chest clear	Dec. 2, 1942	276 mg. intramuscularly over 3½ months	Deposit in manubrium developed during treatment. Nodules became bluish, ulcerated, and later scabbed
2	68	Lump lt. breast noticed 1919. Ulcerated 1934. *X*-ray therapy to numerous areas rt. and lt. breasts, chest wall, and regional nodes Jan., 1939, to Aug., 1942. Recurrent skin nodules Dec., 1942. *No section*	Multiple nodules and induration scattered over rt. and lt. chest wall and sternum. *X*-ray chest—fluid at left base	Dec. 22, 1942	410 mg. intramuscularly over 3 months	Fresh nodules developed. Nodules became more raised and bright red. Uniform scabbing followed. *Biopsy:* Nodule showed highly cellular carcinoma of anaplastic type. Local area of necrosis present at centre of nodule. General condition deteriorated. Died 4 m. after onset of treatment
3	62	Lump in lt. breast noticed Oct., 1939. Treated H.V. therapy Oct., 1940. Diathermy excision residual growth April, 1941. H.V. therapy to recurrence Dec., 1941, and Oct., 1942. Further *x*-ray therapy Dec., 1942. *Section:* Undifferentiated columnar-cell carcinoma	Multiple nodules lt. chest wall. Underlying diffuse oedema from axilla across midline to rt. breast, which was widely infiltrated and fixed	Dec. 30, 1942	676 mg. intramuscularly over 6 months	In 1 month the rt. breast was softer; oedema of chest wall had diminished. Nodules were paler, softer, and smaller. This condition was maintained for 6 weeks, after which the local condition progressed. New crops of nodules developed
4	40	Lump in lt. breast noticed Mar., 1941. Treated *x*-ray therapy Mar., 1942. Recurrence Nov., 1942. *Biopsy:* Anaplastic carcinoma	Ulcer lt. breast 7·5 × 3·2 cm. Regional nodes not enlarged. *X*-ray chest—multiple secondary deposits	Dec. 22, 1942	199 mg. intramuscularly over 2 months	Ulcer increased in size throughout treatment
5	31	Complained of pain rt. hip Sept., 1942. *X*-ray pelvis—large secondary deposit pelvis	Lt. breast—mass 3 × 3 cm. firmly fixed to deep structures. Rt. axilla—2 firm nodes 1·5 cm. across. Pubis—localized tenderness	Jan. 23, 1943	262 mg. intramuscularly over over 7 wks., 252 mg. orally in 6 wks. H.V. therapy to pubis concurrently	Breast—slow increase in size of tumour with development of an adjacent skin nodule
6	49	Lump lt. breast noticed Sept., 1939. Treated H.V. therapy 1940. Recurrence Oct., 1942, treated H.V. therapy. Further recurrence Jan., 1943	Lt. breast—residual mass. Rt. breast—mass 12·5 cm. across. Skin adherent. Fixed deeply. Skin nodules over sternum	Feb. 10, 1943	450 mg. intramuscularly over 5 weeks	Tumour rt. breast progressed. Lt. breast — condition stationary. Secondary deposits in skull developed
7	47	Mass lt. breast noticed July, 1940. Hard nodes rt. axilla and rt. supraclavicular regions. Treated *x*-ray therapy July, 1941, and Oct., 1942. Recurrence Jan., 1943. *No section*	Rt. breast—skin diffusely infiltrated by growth. Rt. side neck—plaque of skin nodules 10 × 6 cm.	Feb. 15, 1943	433 mg. intramuscularly over 7 weeks	Slow progress of disease
8	50	Lump rt. breast noticed June, 1942. Treated *x*-ray therapy Oct., 1942. Recurrence Jan., 1943. *No section*	Rt. breast solid with growth but no deep fixation. Skin densely infiltrated. Reddened nodule 2 cm. across, above nipple. *X*-ray chest—many large secondary deposits lungs. Rt. axilla—hard fixed mass 5 cm. across	Mar. 23, 1943	660 mg. intramuscularly over 4 weeks	Mass rt. breast and rt. axilla increased in size. General condition deteriorated
9	61	Radical mastectomy 1935. Recurrence 1943. Treated *x*-ray therapy Oct., 1943. Recurrence Dec., 1943. *No section*	Nodules rt. chest wall	Dec., 1943	1 mg. daily 3 mths. orally	Many fresh skin nodules developed. Now in local hospital
10	57	Lump rt. breast noticed Aug., 1941. Treated *x*-ray therapy Aug., 1942. Radical amputation in 1942. Recurrence Sept., 1943. *Section:* Highly cellular intra-duct carcinoma	Nodules rt. chest wall, rt. axilla, and rt. supraclavicular fossa	Dec., 1943	1 mg. three times a day orally for 4 months. Still under treatment	After 2 months nodules flatter but size unaltered. In a further month nodules practically gone. After 4 months two fresh nodules developed
11	64	Lump lt. breast 1942. Untreated	Mass lt. breast 12 × 10 cm. with central ulceration. Mass lt. axilla 6·5 × 4·0 cm.	Feb., 1944	15 mg. weekly intramuscularly and 1 mg. daily orally. Still under treatment	In 2 weeks ulcer dry. In 12 weeks mass lt. breast 6 × 5·5 cm. Mass lt. axilla 3·5 × 3 cm. (Fig. 3.) *Biopsy:* Spheroidal-cell carcinoma
12	80	Lump lt. breast 1937. Grew steadily and ulcerated through skin. *X*-ray therapy 1938. Recurred 1939; treated by radium implantation. Recurred 1940	Ulcer 6 × 6 cm. fixed to muscle. *Section:* Cellular carcinoma of pavement-cell type	Sept., 1943	21 mg. weekly by mouth. Total of 315 mg. in 3½ months	By Dec. 24 ulcer reduced in size to 3 × 2 cm. By April 15 two tiny patches ulceration 2 × 1·3 cm. and 1·2 × 1 cm.
13	67	Lump lt. breast noticed Oct., 1943	Bright-red mass lt. breast 9 × 8 cm. fixed to skin and muscle. Large lt. axillary node. *Section:* Papillary adenocarcinoma (malignant intraductal pattern)	Feb., 1944	42 mg. weekly by mouth. Total of 348 mg. in 8 weeks	Breast mass 7 × 7·5 cm., flatter and purplish. Axillary node not changed in size. Slight nausea; gain of 4 lb. in weight
14	68	Radical mastectomy for carcinoma rt. breast 1936. In 1940 noticed lump lt. breast, and enlarged axillary and supraclavicular nodes. Palliative *x*-ray therapy 1940 and 1942. Extensive recurrence Oct., 1943	Massive involvement *en cuirasse* back and front of chest. *Section:* Adenocarcinoma invading subcutaneous tissue	Feb., 1944	42 mg. weekly by mouth. Total of 378 mg. in 9 weeks	Lesions progressed during treatment, and general condition deteriorated

terminated on account of the patient's being transferred to other hospitals, or referred for tumour excision or *x*-irradiation. Two cases which showed undoubted partial regression of the tumour merit special comment.

Case 1: Male aged 74; Carcinoma of Bladder.—The general condition was poor when treatment began. The patient complained of frequency of micturition, passage of blood in the urine, and shooting pains in the back and at the base of the spine. Cystoscopic appearances were typical of carcinoma of the bladder, and *x*-ray examination revealed a secondary deposit in D. 10. The bladder tumour was apparently slow in growth, since a second cystoscopy after 3 months showed little change. Treatment with triphenylchlorethylene was then begun, and was followed by a rapid improvement of the general condition. After 2 months a third cystoscopy showed marked amelioration of the local condition, with almost complete regression of the primary tumour. At this time tissue for diagnosis was taken through the suprapubic route, and doubtful areas in the bladder were fulgurated. An extract from the pathological report (by Dr. L. M. Hawksley) reads: "In the deeper part of the subepithelial connective tissue and in the fibromuscular tissue focal collections of squamous carcinoma cells, which are definitely identifiable as such, though of viable appearance in only one or two places, have undergone almost complete necrosis." The total dosage of triphenylchlorethylene administered was 760 g. over a period of 9 months. The patient died from circulatory failure 11 months after the beginning of treatment. Necropsy confirmed that viable tumour cells remained in the bladder wall after the disappearance of the primary tumour.

Case 2: Male aged 60; Carcinoma of Prostate.—In this case, admitted on account of frequency of micturition and later complaining of shortness of breath and fleeting chest pain, investigation with uroselectan revealed enlargement of the left kidney, with poor function, and a large filling defect in the bladder on the left side. *X*-ray examination suggested the presence of multiple secondary deposits in the bony pelvis, and in the following weeks similar deposits were recorded in the whole of the dorsal spine, in the ribs, femora, and humeri, and in the lungs. Cystoscopy showed enlargement of both lobes of the prostate, with a large papillomatous mass in the left wall of the bladder. Bladder capacity was much reduced (residual urine, 2 oz.). Biopsy at first gave no undoubted evidence of malignancy, but a second specimen (tissue from bladder removed through cystoscope 11 weeks after starting treatment with triphenylchlorethylene) was reported upon as follows by Dr. Hawksley: "Sections show intact and regular but thinned surface epithelium directly overlying a densely cellular mass of columnar-cell adenocarcinoma of prostatic type, in which well-formed gland lumina occur frequently in the solid cell masses. Although no signs of degenerative change are found, the tumour cells show an unusual absence of evidence of nuclear activity, no mitoses having been seen in the numerous sections examined, and the large, spherical nuclei showing a striking uniformity of size and structure."

Treatment with triphenylchlorethylene had been started on June 9, 1941, and soon produced side-effects (bilateral mastitis and oedema of the ankles) attributable to oestrogen action. Within 3 months the total dose administered exceeded 100 g., and the daily dose had reached 8 g. (maximum). The total dose after 6 months was 700 g., following which the daily dose was decreased (to 3 g.) on account of occasional nausea. During treatment there occurred a decrease in the frequency of micturition and some betterment of the general condition, which after 8 months was regarded as considerably improved. There was, however, no unequivocal radiographic evidence of change in the skeletal deposits, as judged by comparison, after repeated examination, of the various regions involved; but the prostate itself was described as "not obviously enlarged" after 13 months, when a total of 1,346 g. of triphenylchlorethylene had been administered. The plasma acid phosphatase values showed a distinct tendency to increase (from 17 units to 47 King-Armstrong units per 100 ml. over 15 months). The case was then transferred for treatment with stilboestrol in place of triphenylchlorethylene, and is included as Case 6 in a paper by Watkinson *et al.* (1944).

In this series of cases of malignant disease other than carcinoma of the breast, treated with triphenylchlorethylene, the number showing any degree of response was very small, and it may be noted that two of those chosen for comment represented types which might reasonably be expected to possess some special sensitivity to the action of oestrogens. Yet this is not invariably the case, and it is probable that a small proportion of tumours, not derived from tissues of any characteristic or obvious endocrine function or susceptibility, may give a similar response.

B. Triphenylmethylethylene

Four cases of carcinoma of the breast and 3 cases of Hodgkin's disease received treatment. The first group (all in advanced stages of breast cancer) were treated for two months or longer by intramuscular injection of the drug, and only one case (pathologically a spheroidal-cell carcinoma) showed any response. This took the form of flattening of the lesions and the development of a blue coloration of the nodules in the skin. In the four cases, total dosage of the drug varied from 1.4 to 3.8 g.

The main points arising during the treatment of the cases of Hodgkin's disease, in two of which biopsies and serial blood counts were taken, were as follows.

Case 1.—A woman aged 42 presented enlargement of the submaxillary, cervical, and inguinal lymph nodes and multiple opacities in both lungs. A biopsy specimen from a node was diagnosed as Hodgkin's disease. When treatment began the blood count was: red cells, 4,580,000 per c.mm.; white cells, 10,000 per c.mm.; total lymphocytes, 1,000 per c.mm. After one month (in which 12 g. of triphenylmethylethylene was given intramuscularly) the blood count had fallen to: red cells, 2,750,000 per c.mm.; white cells, 5,000 per c.mm.; total lymphocytes, 140 per c.mm. The tumours themselves showed no response.

Case 2.—A boy aged 15 showed enlargement of the liver to the level of the umbilicus, of the spleen to that of the anterior superior iliac spine, and involvement of the cervical and hilar nodes. His general condition was very poor. He lived for 2½ months, and during this time received 242 g. of the drug by mouth. After 1 month both liver and spleen were notably smaller, and remained so until accurate observation was no longer possible owing to the development of gross ascites. No diminution took place in the size of the cervical or mediastinal nodes. Conclusions based on the blood picture are not possible, since two transfusions of whole blood were given; but no remission occurred during the period of observation. Necropsy revealed destruction of the pancreatic parenchyma by sarcomatous tissue, in view of which it was thought necessary to designate the condition as malignant—viz., Hodgkin's sarcoma or polymorphic reticulum-cell sarcoma.

Case 3.—A male aged 20 presented enlargement of a single group of cervical lymph nodes. Neither the spleen nor the liver was palpably enlarged. Over a period of 1 month 28.9 g. of triphenylmethylethylene was administered by mouth and 8.6 g. by intramuscular injection. During this time the mass in the neck increased in size. The effects on the blood picture seen in Case 1 of this series were not reproduced, both the red cell and lymphocyte counts remaining stationary. The case was then referred for *x*-irradiation, when the lesions proved to be radiosensitive.

C. Stilboestrol

Table II summarizes the details relating to 14 cases of carcinoma of the breast treated with stilboestrol: the most favourable response is shown in Fig. 3 (Case 11). Whether or not by chance, this small series provided a slightly lower proportion of cases showing any marked effect in the shape of changes in the growth and behaviour of the tumour. Assuming such changes to be related wholly to the oestrogenic activity of a given compound, there is no reason to suppose that the repeated administration of stilboestrol, which affords the advantage of effective action in very low dosage, will be less effective in producing them than is continued treatment with triphenylchlorethylene, but rather the contrary. In a few of the present cases treated with triphenylchlorethylene or triphenylmethylethylene administered orally, Mr. F. L. Warren was able to recover from the faeces over 90% of the dose given in a measured period (usually 24 hours). This indicates that the drug absorption is relatively inefficient, and probably highly so when compared with stilboestrol. There remains the possibility that some advantage may accrue from the use of compounds of exceptionally long duration of action (as judged by the persistence of their oestrogenic effects): several such compounds are now available, and this suggestion is being explored.

It is clear that the cases now reported afford no contribution to effective therapy, but they are probably sufficient in number to set the subject, as it stands at present, in a fair light. The results, although illustrating well the special difficulties inherent in the problem, have considerable fundamental interest, and at least provide an incentive to further investigation.

Summary

73 cases of advanced cancer received treatment with the synthetic oestrogens triphenylchlorethylene, triphenylmethylethylene, and stilboestrol.

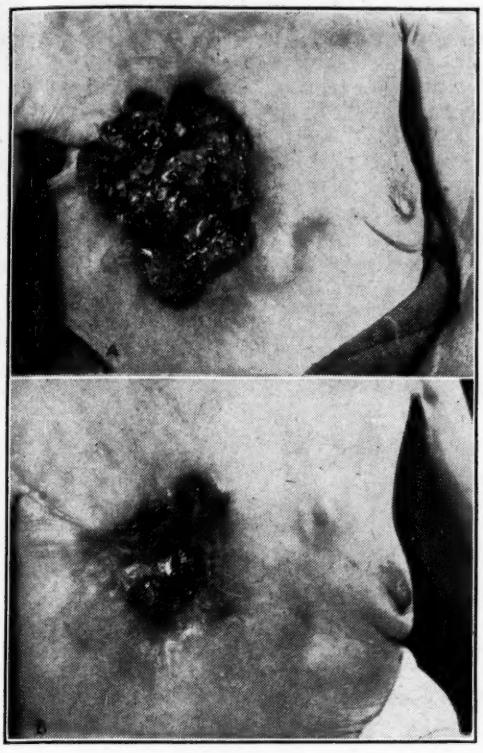

FIG. 1.—*Case 1 (Table I). Carcinoma of Breast.* The primary lesion (A) at May 20, 1941, and (B) at Oct. 29, 1941, after treatment with triphenylchlorethylene.

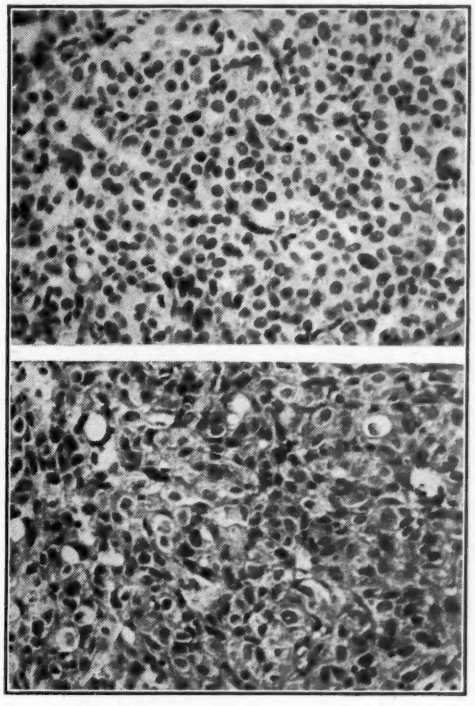

FIG. 2.—Histological section, Case 18 (Table I). Above:—Before treatment with triphenylchlorethylene. H. and E. ×300. Below:—After treatment for 1 month. Note irregularity in size, shape, and staining of nuclei. H. and E. ×300. Sections stained together.

Of 22 cases of late malignant disease of the breast treated with triphenylchlorethylene (usually in doses of 3 to 6 g. per day), 10 showed a significant although temporary retardation, or even partial regression, of the growth of the tumour. No evidence was obtained to suggest that the drug will prevent the development of metastases. The initial effect of treatment in these cases passed off comparatively rapidly, and only one has shown prolonged arrest, the ultimate course of the disease being in no way altered in the remainder. The degree of retardation was less than could be expected from local palliative *x*-irradiation.

Of 30 cases of advanced malignant disease other than cancer of the breast (including carcinomata of the skin, maxillary antrum, urinary bladder, ovary, rectum, and testis, with reticulo-endothelial growths and leukaemia), and similarly treated with triphenylchlorethylene, only 2 (carcinoma of the bladder, carcinoma of the prostate) showed undoubted partial regression of the tumour.

Of 4 cases of mammary cancer and 3 cases of Hodgkin's disease treated with triphenylmethylethylene (usually by intramuscular injection) only one (spheroidal-cell carcinoma of the breast) showed even a temporarily favourable response.

Of 14 cases of carcinoma of the breast treated with stilboestrol (by intramuscular injection or by mouth over a period of several months), 5 showed alterations in the growth and behaviour of the tumour similar in nature to those produced by triphenylchlorethylene.

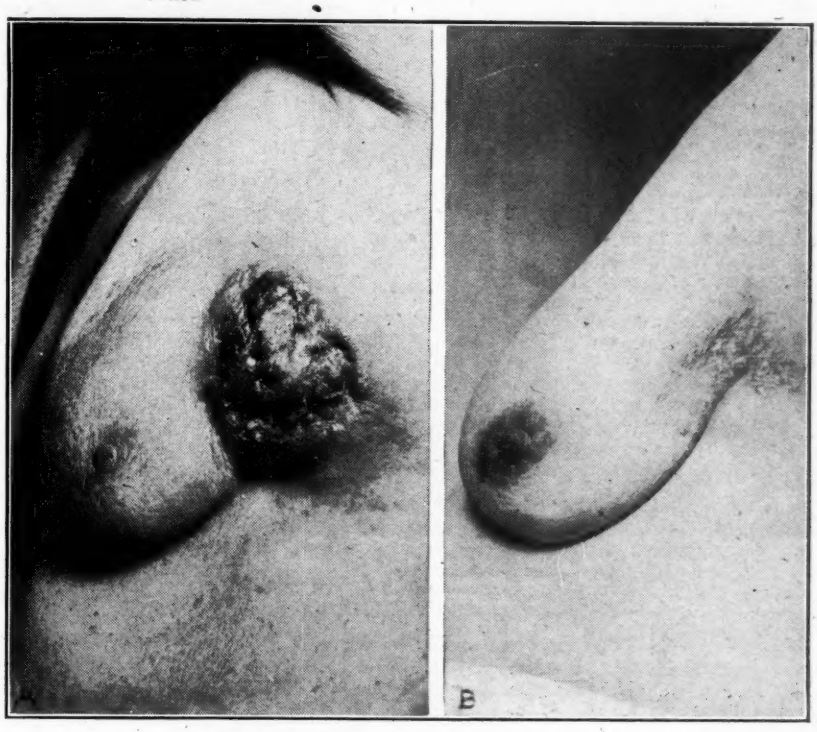

FIG. 3.—*Case 11 (Table II). Carcinoma of Breast.* The primary lesion (A) at Feb. 7, 1944, and (B) at May 22, 1944, after treatment with stilboestrol.

Serial biopsies in a few cases with a marked clinical response showed histological alterations (diminution of mitosis rate, variations of staining behaviour, and necrotic changes) of a type not resembling the changes following *x*-irradiation.

The secondary signs of drug action included nausea, pigmentation of the mammary areola, mastitis in the male, uterine bleeding, and oedema of the lower extremities. One or more of such changes occurred with special frequency in cases showing some degree of tumour regression. Several of these cases also manifested improved appetite, gain in weight, and diminution of pain.

This investigation has been supported by grants, for which we express our thanks, from the British Empire Cancer Campaign and the Anna Fuller Fund. We are also indebted to the Medical Com-

mittee of the Royal Cancer Hospital (Free) for permission to publish details of those cases under their charge, and to Imperial Chemical Industries Ltd. (Dyestuffs Division) for supplies of triphenylchlorethylene and triphenylmethylethylene.

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ADDENDUM.—CYTOLOGY OF SERIAL BIOPSIES FROM A CASE OF CARCINOMA OF THE BREAST TREATED WITH STILBOESTROL

BY

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The following is a summary of the cytology of serial biopsies from Case 11 (carcinoma of the breast, Table II, above) taken during a period of markedly favourable response (tumour regression) after treatment with stilboestrol.

Biopsy I. Before Treatment: Feb. 7, 1944

In respect of nuclear morphology two main cell types could be distinguished in the resting stage. One is characterized by a nucleus which contains several Feulgen-positive chromocentres (the potentially dividing cell). The other has a nucleus with one large or several small nucleoli (the differentiated cell). The proportion of potentially dividing cells in different regions of the biopsy material was found to vary between 12.5 and 27.3%. The division rate was determined in four cell populations (600 cells in each) taken from different regions of the specimen: in these the division rate was found to be 2.3, 5.2, 5.6, and 7.5%. Synchronous division of three or four tumour cells was frequently observed. Chromosome behaviour and spindle formation were normal. The highest incidence of degenerated cells was 2.5%.

Biopsy II. March 10, 1944 (Treatment started Feb. 9, 1944)

Nuclear and cytoplasmic changes were observed. Cells were found with one or more vacuoles in the nucleus, which latter gave a weakly positive Feulgen reaction. The frequency of such cells varied between 4 and 7.5% in different regions. Other abnormal cells were seen with deeply staining cytoplasm. The division rate was apparently lower in this biopsy specimen as compared with Biopsy I: the highest division rate found was 4.6%. In some dividing cells chromosomes were seen lying off the equatorial plate, and these were shorter and thicker than usual. While there appeared to be a decrease in division rate, a significant increase was observed in the proportion of degenerated cells. In one region it was found to be 12.5%. The morphology of the degenerating cells differs from that of cells degenerating as the result of x- or gamma-radiation.

Biopsy III. During Treatment: April 25, 1944

The number of cells showing nuclear and cytoplasmic alterations has further increased. Division rate was estimated to vary between 4.2 and 5.6%. Apart from chromosome lagging at anaphase in a few dividing cells, no other mitotic abnormalities were seen. The frequency of degenerating cells was about the same as in Biopsy II.

Biopsy IV. During Treatment: May 29, 1944

The biopsy material shows marked alterations. The division rate has increased and regions were encountered with 14.3% of cells in division. Synchronous division of several adjacent cells was very frequent. The chromosomes of cells in mitosis were thick and short, they failed to form an equatorial plate at metaphase, and were scattered in the cells. Cells with multipolar spindles were also encountered. The proportion of degenerating cells was found to vary between 7.3 and 16.3%. While the cellular abnormalities and the various stages of cell necrosis observed in the second and third biopsies indicated that cell degeneration is brought about by nuclear vacuolization, evidence was obtained from this fourth specimen that cell degeneration may also be due to a breakdown of the mitotic mechanism. The cytological evidence thus suggests that the primary effect of stilboestrol in this case may be localized to the nucleus of the tumour cell.

REACTIVE HYPERINSULINISM

CASE REPORT, WITH A DISCUSSION OF THE DIFFERENTIATION FROM ISLET TUMOUR

BY

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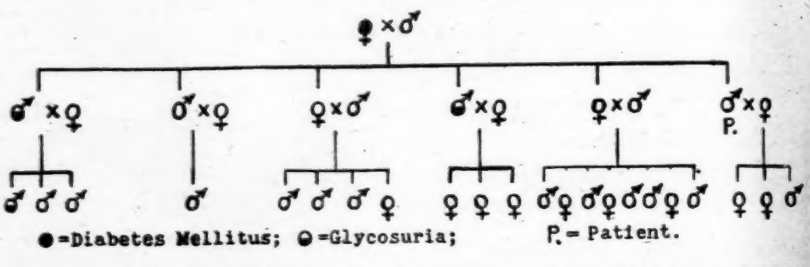
The condition known in this country as "hypoglycaemia" (Cambridge, 1924) is described under the term of "hyperinsulinism" or "dysinsulinism" in America, according to the manifestations encountered—dysinsulinism implying an erratic under- and over-secretion of insulin (Harris, 1934). According to this terminology, hyperinsulinism would not include hypoglycaemia due to hepatic damage. The conditions here to be discussed are those in which the pancreatic activity is mainly at fault, and therefore exclude those due to other glandular dyscrasias and hepatic disease. It is the object of this communication to draw attention to a condition which may be termed "reactive hyperinsulinism," as opposed to hyperinsulinism due to overactivity of the pancreas as a result of tumour of the islets, malignant or benign. The term "reactive hyperinsulinism" is to be preferred to that of "functional hyperinsulinism" of Conn (1940), since the word "functional" has other less well defined associations.

Case Report

A professional man aged 56 complained of attacks consisting of a sinking feeling during the preceding five years and of continual tiredness for four years. He had had three attacks of arthritis, mainly affecting the larger joints, in the course of ten years. The family history was noteworthy (see genealogical chart). The patient's mother had died of diabetes mellitus, but the father was a healthy man, and lived to the age of 84. The eldest brother had renal glycosuria, and his eldest son has been found to have glycosuria. A second brother has also had glycosuria for many years, recently having had an operation for cataract. There are also a healthy brother and two sisters.



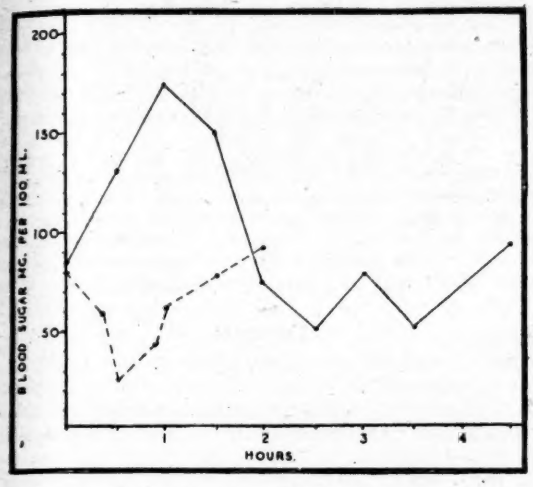
The patient stated that for the last four years he had had a continual feeling of tiredness accompanied by considerable difficulty in concentrating. During this period his work had greatly increased and his hours had been long, with short intervals for meals. For five years he had had acute attacks consisting of a sinking feeling in the epigastrium and intense weakness, followed by a cold sweat. He was forced to sit down during the attacks, but never fainted. After the attack had passed off his appetite was ravenous. The attacks always occurred in the afternoon or early evening, about three hours after the last meal. It appeared that his wife had been in the habit of "fortifying" him daily with a large tea consisting mainly of carbohydrate, including a great amount of honey or jam. Furthermore, the greater the quantity of such food consumed the greater the severity of the subsequent attack. The attacks passed off spontaneously with rest for about ten minutes or on taking carbohydrate. Their frequency was variable, six weeks sometimes elapsing between them, at other times two occurring in a week. In general their frequency and severity had increased with the passage of time. Occasionally exercise—e.g., gardening—brought on an attack, but only at the time of day already mentioned. Usually he could take considerable exercise and little food without getting symptoms. He had had no polydipsia or polyuria and no headache. He had lost one stone in weight in three years.

On examination the patient was not obese. There were no physical signs and no evidence suggestive of glandular or hepatic disease. Circumstances did not permit of special investigations of liver function, but the blood-sugar curve does not conform to the type seen in hepatic disease. There was no glycosuria.

Investigations of Blood Sugar

A month before he was seen reports on his blood sugar were: 8 p.m. (during an attack), 48 mg. per 100 ml.; 14 days later, at 8 a.m. (before breakfast), 71 mg. per 100 ml. At 8.30 a.m. a carbohydrate breakfast was taken; at 10 a.m. the blood sugar was 90 mg. and at 11 a.m. 66 mg. per 100 ml., the value at 12 noon being the same.

While in hospital the blood sugar was found to be 85 mg. per 100 ml. on two occasions before breakfast. Immediately after lunch the value was 87 mg. per 100 ml. The patient then took a rapid two-hour walk in hilly country, producing a moderate degree of fatigue, and at the end of this time the blood sugar was 97 mg. per 100 ml. The accompanying Graph shows the results obtained with



Continuous line represents glucose-tolerance test: 50 g. glucose orally after 12 hours' fast. Dotted line represents insulin tolerance: 6 units of insulin intravenously, fasting.

glucose-tolerance and insulin-sensitivity tests, the patient at the time receiving a full ward diet. There was no glycosuria during the glucose-tolerance test. Typical symptoms of one of the patient's hypoglycaemic attacks occurred when the blood sugar had fallen to 48 mg. per 10 ml., and persisted for one hour. The symptoms consisted of blurring of vision, the distant appearance of near objects, difficulty of finding words in speech or writing, inability to concentrate, coldness and clamminess, and a sinking feeling in the epigastrium. The insulin-tolerance test showed a slight increase of sensitivity to insulin. During this test there was another typical hypoglycaemic reaction when the blood sugar had fallen to 40 mg. per 100 ml. The symptoms disappeared without intervention, and there was no question of the patient's approaching a comatose state.

A diagnosis was made of reactive hyperinsulinism due to excessive insulin response resulting from the stimulus of administered carbohydrate. The patient was advised to cut down the consumption of carbohydrate at tea and replace this with protein or fat—e.g., in the form of an egg—if necessary. Having reduced the consumption of potato for lunch and dinner, together with the omission of jam or honey and curtailment of bread-and-butter and cake at tea, the patient has experienced no further attacks over a period of twelve months. This is in spite of the fact that his work has continued as before.

Discussion

The chief differential diagnosis in this case is from organic hyperinsulinism due to tumour of the pancreatic islets, which if present might be malignant. A search of the literature reveals that there is a lack of criteria for establishing this diagnosis (see especially Harris, 1936–7). However, there are apparently certain points that may be of diagnostic value. For instance, Conn (1940) considers that the presence of a low value for the fasting blood sugar before breakfast, the diet being normal, is a point strongly in favour of organic disease. It is well known that there is no relation between the blood-sugar level and the severity of a hypoglycaemic attack, although many of the cases do in fact have such attacks at this time. The second point for special examination is the shape of the glucose-tolerance curve. Conn and Conn (1941) consider that in "functional hyperinsulinism" the blood-sugar level shows a precipitate fall after a large amount of carbohydrate. Examination of the case reports of Finney and Finney (1928), Feinier *et al.* (1935–6), and Fraser *et al.* (1938) show, for example, sugar-tolerance tests of the "plateau type." Whipple *et al.* (1941) in an analysis of 17 cases due to tumour found that the curve had a decided trend towards the diabetic type, this presumably being a manifestation of dysinsulinism. Their average figures showed a resting value below normal, with a subsequent persistent blood-sugar level of about 150 mg. per 100 ml. for a period of two to three hours. However, in their report two cases diverged from this type and gave low flat curves—a finding also observed by Conn and Conn (1941).

There are fewer reports available on the value of the insulin tolerance. Hartmann and Jaudon (1937) found an unusual sensitivity to insulin in newborn hypoglycaemic children whose mothers were diabetic, the hypoglycaemia being due to prolonged foetal islet stimulation. Furthermore, the findings of Fraser *et al.* (1938) in a case of islet tumour are so striking, and in such contrast to those in the present case, that they merit further study. Those authors found that, although the sensitivity to insulin was approximately normal, there was no tendency for the spontaneous recovery of the blood sugar within two hours. The injection of insulin in the fasting state was a reliable means of producing a severe hypoglycaemic reaction which only terminated on the administration of adrenaline or glucose. The finding of the adrenaline sensitivity is opposed to the views of Wilder *et al.* (1927)—who were supported by Allen (1941)—that resistance to adrenaline is a diagnostic point in favour of tumour. Cammidge and Poulton (1933), commenting on the case reported by Griffiths and de Wesselow (1933), pointed out that this test may be difficult to interpret.

A final point that may be of value in the differential diagnosis is the severity and irregularity of the symptoms. In general it appears that the more severe they are, without any tendency to spontaneous alleviation if glucose is not given, and the more irregular their onset, the more likely is organic disease. Conn (1940) and Harris (1936–7) both gave criteria indicating the necessity for laparotomy, the latter author suggesting that the inability to control the attacks by diet within a few weeks should be taken into account. Allen (1941) considered that the ability to control symptoms by means of a high-protein diet is indicative of but a mild degree of insulin excess. However, in view of the malignancy of carcinoma of the pancreatic islets and the inoperability consequent upon the occurrence of metastases, it is clearly essential to establish criteria for laparotomy requiring as short a period of observation as possible.

The following summarizes the features of the present case for contrast with the foregoing points:

1. Absence of low fasting blood sugar before breakfast and after exercise.

2. The marked post-prandial fall in blood sugar during the glucose-tolerance test, accompanied by the onset of symptoms of hypoglycaemia, together with an instability of the blood-sugar-regulating mechanism for a period of two hours. This finding is in close agreement with the history obtained of the most severe attacks occurring after the largest amounts of carbohydrate had been taken for tea.

3. A slight increase in the sensitivity to insulin, the occurrence of a typical hypoglycaemic attack after intravenous administration of insulin, and the spontaneous return of the blood-sugar level to normal limits with disappearance of symptoms.

4. The mildness and ease of control of the symptoms by means of reduction in carbohydrate intake.

5. The family history of diabetes and renal glycosuria.

In connexion with the last of the above points the case of MacPherson (1941) may help to throw some light on the aetiology of these attacks. His case showed a sugar-tolerance curve resembling that in the present case. In addition to this his patient had renal glycosuria—a condition recognized as occurring with, and possibly playing a part in the production of, "functional hyperinsulinism" (Conn, 1940). MacPherson suggested that two of the precipitating factors in his case were irregularity in meals and hard work. In the present case it appears from the history that there was some definite relation of the onset of symptoms to increasing severity of work and to increase of worry. Although humoral mechanisms are involved in the control of blood-sugar levels, Wauchope (1933) and Conn (1940) indicated that imbalance of the autonomic

nervous system may have a bearing on the production of "functional hyperinsulinism." Cori (1931) in an extensive review concluded that vagal impulses play a part in the finer regulation of the insulin production, and Cannon *et al.* (1924) have shown that nervous control of the adrenal medulla via the splanchnic nerves ensures a rapid adrenaline response.

It can well be appreciated how the continuance of abnormal stress in a susceptible individual may give rise to abnormality or instability in the control of these opposing impulses by the hypothalamic region. The terminal stages of the glucose-tolerance test is illustrative of this.

Summary

A case of "reactive hyperinsulinism," manifest by an excessive post-prandial fall of the blood-sugar level, is described. Points in the differential diagnosis from hyperinsulinism due to tumour of the pancreatic islets are discussed.

My thanks are due to Dr. H. Gardiner-Hill for his interest and permission to publish this case, and to Dr. C. Ede for assistance, especially with the history.

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TRAUMATIC RUPTURE OF THE AORTA

BY

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The following case of rupture of the aorta due to a blow on the epigastrium presents clinical and pathological features interesting enough to be placed on record.

Clinical History

The patient was a farmer, aged 37, who was described by his relatives as being in robust health. He had no relevant medical history, but his family doctor had observed that he had a very high threshold for pain. On Jan. 20, 1944, he went ploughing at 1 p.m., and at 3 p.m. left the field to call at a neighbouring farmhouse for a drink of water. He there complained that shortly before that time his plough had struck a stone, and the plough handle, rearing up, had hit him somewhere in the region of the praecordium. The blow had shaken him badly, and from statements he made to various people it appears that immediately after the accident he felt very ill, owing presumably to shock; but he soon recovered, continued to plough till about 4 p.m., and made no further reference to the accident He returned home at 5 p.m., when he complained of pain in the left side of the chest radiating through to his back. It was observed that he was cold, clammy, and pale, and he had to go to bed. He was examined later the same evening by his doctor, who found that his temperature was 100° F. and that friction could be heard in the cardiac area. The patient made no reference to the accident, and his doctor was in complete ignorance of the incident till after the man died. He passed a restless night because of chest pain, and vomited three times. Next morning the pyrexia had disappeared, and though he still complained of pain he did not seem to be particularly ill. His condition remained much the same till late afternoon, when he died suddenly within a few minutes of sitting up in bed to drink a cup of tea.

Post-mortem Findings

The deceased was well built and there was no external evidence of injury. No bones were broken. There was an area of bruising in the areolar tissue of the anterior mediastinum, and the bruising extended up the right side of the neck as far as the level of the larynx in the line of the great vessels and sterno-mastoid muscle. The pericardial sac was distended with blood, which had infiltrated the wall, particularly in the region of the base of the heart. On the posterior wall of the first part of the aorta there were three tears in the vessel—one just above the valve cusps, a second at the beginning of the arch, and a third midway between the first two. The upper tear was half an inch and the others each a quarter of an inch in length. All the tears were oblique to the transverse axis of the vessel, but were not parallel to one another. The aorta was not dilated, and the only abnormality was some early atheroma, which appeared as small patches hardly elevated from the general level of the intima and free from calcification and ulceration. The heart weighed 28 oz. (793.5 g.), but the hypertrophy was evenly distributed throughout all the chambers; there was no dilatation; all the valves were competent and their cusps healthy. The heart muscle was of excellent tone and free from all sign of disease, both on gross examination and microscopically, but the individual fibres were hypertrophied. The coronary vessels were capacious, and on the left one there were a few small patches of early atheroma, but quite insufficient to interfere with the blood supply. The right coronary artery was healthy.

In the peritoneal cavity there was a little slightly blood-stained serum. On the posterior abdominal wall some haemorrhage could be seen shining through the peritoneum in the region of the pancreas. The left half of the body and tail of that organ were haemorrhagic, but no fat necrosis was anywhere observed. The other structures in this cavity were uninjured. The only abdominal disease found was an early hydronephrosis of the left kidney, and, though the entire urinary tract was dissected, no satisfactory explanation was discovered for this abnormality. There was no sign of chronic nephritis or any significant abnormality in other structures.

Comment

Contusion and rupture of the pancreas are relatively rare injuries. Vance (1928) quotes Gall to the effect that they occur in 4.4% of all visceral injuries, and most other authors agree with this figure. The pancreas lies in such a position that it could only be injured, in the absence of an open wound, by some hard object coming forcibly in contact with the epigastrium and crushing the gland against the body of the second lumbar vertebra. It is possible, however, that the view of Boesch (1921) is correct—namely, that the gland may frequently be injured without the condition being recognized during life. This case tends to support that view, as the patient made no complaint referable to the abdomen and was neither rigid nor tender in that region. Furthermore, the fact that fat necrosis was not present indicates that the pancreas was contused and not ruptured, and it seems likely that the condition might have resolved and remained unrecognized had the patient not sustained other more serious injuries which proved fatal.

It is clear, then, that the handle of the plough struck him a deep, powerful blow in the epigastrium. There were no injuries of any kind to the thoracic wall in the shape either of subcutaneous or muscular bruises or of fractures of the ribs or sternum, and it is almost inconceivable that a relatively sharp object like a plough handle could strike that region with enough force to produce the internal injuries described without leaving some mark on the soft tissues or the thoracic cage. It follows, therefore, that the damage to the aorta must have been produced indirectly by transmission of the force through the diaphragm. This thesis is supported by the fact that the anterior mediastinal tissues were contused in the absence of more superficial damage, the bleeding being no doubt due to the rupture of small vessels consequent upon the sudden dislocation of the pericardial sac. The heart is suspended in the pericardium by the aorta and superior vena cava, but is given basal fixation by the inferior vena cava and the structures of the lung roots. Its potential mobility is strictly limited in all directions, and it seems unlikely that rupture of the aorta alone could occur, due purely to displacement of the heart and traction on the vessels, by a force applied to the diaphragmatic surface of the heart from the abdomen.

Ruptures of the aorta are relatively frequent, but when they occur it is nearly always as a result of crush injuries, in which the osseous structures of the thoracic wall may or may not be fractured, depending largely on their elasticity. The tear is usually transverse, and is located just above the aortic valve cusps. It is due to a force thrusting the heart downwards and tearing it from its points of suspension. In these cases, as a rule, the tear is complete and the outcome immediately fatal. Partial ruptures—which become complete later—are more uncommon, and may arise in the absence of trauma if the

requisite predisposing factors are present. Peery (1942) has recorded the finding of healed partial tears in the first part of the aorta. According to him, partial tears are usually encountered in the ascending portion of the arch, are usually transverse or oblique, and are rarely longitudinal. An essential predisposing factor, in Peery's opinion, is severe hypertension of long standing, and he is not certain that there need be any abnormality in the wall of the vessel. Microscopical sections from the aorta taken near the lesion, but not including it, usually do not show any recognizable abnormality. Arteriosclerosis is probably not a cause for this condition, since the tears seldom occur through an atheromatous plaque or ulcer. The precipitating factor in most cases is exertion, which, by raising the already elevated blood pressure, exceeds the pressure the aortic wall can stand, and rupture occurs.

Another predisposing condition is the presence of coarctation of the aorta, in which the vessel tears below the constriction, presumably owing to the increased pressure in that part of the artery (Moragues, Moore, and Rossen, 1942).

A few cases of partial rupture of the aorta have been recorded in which trauma was the immediate cause. In Heller's (1904) case the partial tear was due to a heavy burden falling on a man's chest. In the case reported by Oppenheim (1918) clinical manifestations followed a blow by a falling piece of granite. Nordlander (1925) and Oppenheim (1918) both referred to the occurrence of ruptured aorta in aviators falling from a high altitude.

The present case is unusual, if not unique, because of the method of production of the damage to the vessel. This man had a grossly hypertrophied heart, and, though his blood pressure was never recorded and there were no symptoms or other post-mortem changes to suggest it, he probably suffered from essential hypertension, though the fact that he had followed a strenuous occupation may have been partly responsible for the hypertrophy. There is no such lesion now recognized as idiopathic cardiac hypertrophy in an adult, and, in the opinion of Kugel and Stoloff (1933), it appears doubtful whether there is such a condition in infants and young children, as some workers maintain. The heart, as stated, weighed 793.5 g. According to Aschoff (1924) the normal heart weight in men is up to 355 g., while Parkinson (1936) quotes Evans to the effect that the upper limit is 390 g. By either of those standards this heart was grossly hypertrophied, and though many hearts weighing more have been reported (Strong and Munroe, 1940; Rosenow and Smith, 1939; and Royster, Lisa, and Carroll, 1941) some other factor in addition to essential hypertension has usually been present to account for the hypertrophy. The mechanism of production of the aortic lesions therefore seems to have been the increased pressure in that vessel. The sudden compression of the heart must have further raised the already high pressure in the left ventricle and aorta to such a degree that the vessel wall was incapable of withstanding it, and partial rupture ensued.

The clinical symptoms in cases of partial rupture of the aorta are always indefinite, and the literature does not seem to record a case in which this condition has been diagnosed ante mortem. According to Peery (1942), "the most common symptom is a choking sensation or a feeling of suffocation. Dyspnoea may come on suddenly and continue for some time. Pain is also a frequent symptom, and may be stabbing or tearing, although pain is less frequent and less severe when dissection supervenes immediately. Occasionally cough, haemoptysis, and fever are the presenting symptoms, and may be associated with pain of pleuritic type. The most important physical finding is undoubtedly the presence of heart murmurs. These may be either systolic or diastolic, and are usually best heard in the aortic area. The systolic murmur is as a rule harsh, and is probably due to vibration, in the blood current, of the abrupt shelf-like edge of the tear, or to eddying of blood over the small pouch between the lips of the tear. In a considerable proportion of cases, however, dissection of the aorta occurs days, weeks, or months later, with the usual manifestations of the condition. In other cases the clinical picture becomes one of aortic regurgitation with congestive heart failure." In the present case there was no immediate pain referable to the thorax, and two hours elapsed before pain started. Probably during that time dissection was not occurring and the acute pain in the left side of the chest radiating through to the back became manifest when dissection through the media began to develop. Final rupture 26 hours after the original injury is in keeping with other cases reported and, as in a proportion of these, it occurred after some mild exertion—in this case sitting up in bed.

It is interesting to speculate what the outcome might have been if the patient had stopped work after the injury and gone to bed. Perhaps the intimal tears might have healed, as happened in the cases reported (Peery, 1942).

Many cases have been recorded in which hypertension has been associated with a unilateral renal lesion of some sort, and hydronephrosis is one of the conditions mentioned. Baggenstoss and Barker (1941) have reviewed the literature and reported a series of their own cases. Their series is short and, they admit, insufficient to draw statistical conclusions in the case of hydronephrosis, but they nevertheless tend to the opinion that this condition does not appear to influence the onset of hypertension. This aspect of the case is mentioned merely for the sake of completeness, in view of the work of Goldblatt (1940) and of Wilson and Byrom (1939) on the relationship between unilateral renal ischaemia and hypertension.

Summary

The clinical and pathological features of a case of rupture of the aorta due to a blow on the epigastrium are discussed.

Gross cardiac hypertrophy and essential hypertension are considered as factors in the mechanism of production of the aortic lesion.

The aetiology and symptomatology of partial rupture of the aorta are reviewed.

My thanks are due to Dr. James McCartan of Sheffield for particulars of the clinical history of the patient.

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A FATAL CASE OF PURPURA AFTER SULPHAPYRIDINE

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An opportunity recently occurred of making observations on a case of acute purpura occurring during the course of sulphapyridine therapy for pneumonia. As we have found records of only 18 cases in the literature, this seems to be one of the rarer complications of sulphonamide administration. For this reason we report the essential details of the case.

Case Report

On Oct. 12, 1943, a publican aged 52 became ill with a febrile condition diagnosed as pneumonia. Sulphapyridine was administered outside hospital, 30 g. being given in seven days. The immediate response was satisfactory, but five days after cessation of treatment a rise of temperature gave cause for anxiety. Recrudescence of pneumonia or empyema was considered. Sulphapyridine therapy was restarted, 4½ g. being given during the next five days. The malaise and pyrexia, however, persisted. It was noted that the temperature rose after each dose of sulphapyridine. On Oct. 28 there was slight

* Working on behalf of the Medical Research Council.

epistaxis. The patient was admitted to hospital on Oct. 30 for investigation.

Apart from trench fever in the last war the patient had enjoyed good health. He had not been subject to asthma, hay-fever, or urticaria; he had never taken sulphonamide drugs previously; and there was no personal or family history of a haemorrhagic diathesis. He was a heavy beer-drinker. An obese heavily-built man, he showed some difficulty in maintaining attention. Mucous membranes were pale. Temperature was 101.6°. The fundus oculi had some arterial thickening, but there were no haemorrhages. The nose was bleeding. There was much oral sepsis. B.P. 205/120. The chest revealed signs interpreted as those of a resolving right lower lobe pneumonia. Spleen and liver were not palpable. There was no enlargement of peripheral lymph glands.

By Oct. 31 the temperature was subsiding, and on Nov. 1 had become normal. B.P. was now 160/110. On this day an extensive purpuric eruption appeared on the palate, arms, and legs. Epistaxis persisted, and blood was oozing from the gums. Three times during the day he vomited coffee-ground material giving a positive benzidine reaction. The urine, normal in quantity, had become frankly blood-stained. The ankles presented pitting oedema.

On Nov. 2 his condition showed further deterioration. Purpura was even more gross, and blood was flowing freely from the nose and mouth. There were many submucous haemorrhages in the mouth, and in the tongue they were particularly well marked. Haematemesis and haematuria persisted. Sternal puncture was performed, and compatible blood was transfused through the site of puncture. As the procedure was started the patient complained of a bursting sensation in the head: 2½ hours later he was in coma. Respirations became laboured and gurgling, and blood-stained saliva was coming from his mouth. The fundus oculi, which earlier in the day had been clear, now showed numerous flame-shaped haemorrhages. There was a left hemiplegia, and plantar responses were bilaterally extensor. B.P. was 260/140. In a further 2½ hours coma had become profound. Fundal haemorrhages were more pronounced and blurring of the disk margins was observed. There was a flaccid paralysis of all the limbs. A finger-prick, made 2½ hours before, was still bleeding freely. Death rapidly supervened.

Investigations

X-ray chest, Nov. 1:—Left ventricle enlarged. Aorta unfolded. The appearances in the lung fields suggested bilateral recent resolving pneumonia. *Sputum* showed a scanty growth of *Strep. pneumoniae* and neisseriae. *Haematology*, Nov. 1:—Erythrocytes, 2,500,000 per c.mm.; Hb (Haden), 47% (7.33 g. per 100 c.cm.); C.I., 0.94; reticulocytes, less than 0.1%. Leucocytes, 10,000 per c.mm.: 3,200 lymphocytes, 6,000 neutrophil polymorphs, 500 eosinophils, and 300 monocytes. Platelets, 150,000 (direct method, using Lempert's modification of Kristenson's technique). Bleeding time (Duke's), 36½ min. (normal 2–5 min.); coagulation time (Lee and White), 27 min. (normal 5–8 min.); clot retraction, 1 hour (Macfarlane), 19% (normal 44–66%). Capillary resistance test by a positive-pressure method indicated very marked fragility. Smears of sternal marrow revealed no grossly abnormal features, except some preponderance of the myeloid elements. Megakaryocytes were present (0.4%), and these appeared normal. The leuco-erythrogenetic ratio was 4.1. *Biochemistry* (7 hours ante mortem):—Plasma urea. 214 mg. per 100 c.cm. Plasma uric acid, 7.3 mg./100 c.cm. Plasma proteins, total 6.4 g./100 c.cm., of which 3.3 g. was albumin, 2.6 g. globulin, and 0.5 g. fibrinogen. Plasma bilirubin, less than 0.5 mg./100 c.cm. Plasma sulphapyridine: free 2.1 mg./100 c.cm.; total 4.44 mg./100 c.cm.

Urine Analysis.—On admission the urine was acid in reaction and contained albumin. The specific gravity was 1008. The centrifuged deposit showed only occasional leucocytes. Haematuria appeared on Nov. 1 and persisted. A sample passed 6 hours before death had a specific gravity of 1007, and albumin was present. There was no urobilinuria. Microscopy of the deposit revealed large numbers of red blood cells. Leucocytes were 6 per h.p. field, and there were very numerous coarsely granular casts.

Necropsy.—(34 hours after death; Dr. C. Keith Simpson.) The heart showed subpericardial, myocardial, and endocardial haemorrhages. Coarse purpuric haemorrhages were present throughout both lungs, causing extensive coarse nodular consolidation. No superimposed infection could be established. There was extensive purpura throughout the alimentary tract, mainly subperitoneal and with but little actual bleeding. The liver showed some purpura. Pulp haemorrhages were present in the spleen. Both kidneys were shot with innumerable purpuric haemorrhages resulting in virtual infarction. The renal pelves, ureters, and bladder contained no crystalline deposits and there was mild purpura only. The brain showed coarse purpuric haemorrhages into the cortex, into the white matter, including a vast area of confluent purpura in the right frontal lobe, and also into the ventricular system.

Histology (J. C. W.)—*Lungs:*—The essential lesion was a widespread haemorrhagic consolidation, mainly confluent. Intervening areas were emphysematous, acutely oedematous, or collapsed. Infiltration of the alveoli by inflammatory cells was observed only at the periphery of the haemorrhagic areas. There was no unresolved pneumonia. The pulmonary capillaries were congested, particularly subpleurally. In some capillaries the endothelial lining cells were swollen. Myocardium revealed only scattered haemorrhages. *Liver* showed no gross pathological change. *Spleen:*—The splenic pulp contained scattered areas of haemorrhage, particularly in the subcapsular region. Moderate amounts of haemosiderin were demonstrated in the splenic pulp. *Kidneys:*—There were multiple haemorrhages. These were especially numerous in the subcapsular region, and formed wedge-shaped extensions into the deeper parts of the cortex. Focal areas of round-celled, mainly plasma cell, infiltration were scattered throughout. These bore no relation to any particular structure. The glomeruli were free from pathological change apart from slight thickening of the capsular basement membrane and occasional distension of the capsular space by red blood cells. There was considerable degenerative change in the epithelium of both convoluted tubules. A few of the collecting tubules contained acidophil hyaline material but no crystals. The interlobular arteries showed hyperplastic thickening and the afferent arterioles a slight degree of hyalinization. There was some increase in renal interstitial tissue, and large numbers of effete red cells were present. Little increase in collagen or reticulin could be demonstrated. Haemosiderin was practically absent.

Sections of femoral bone-marrow showed no architectural change.

Diagnosis

This patient's fatal illness could be attributed to the effects of sulphapyridine. The original lesion was a pneumonia, and the bleeding tendency did not become apparent until 16 days after the onset of this illness. At necropsy the pneumonia had resolved. A bleeding diathesis may be associated with nitrogen retention. In our case the plasma urea was 214 mg. per 100 c.cm. Though he was a hypertensive subject, the kidneys showed only moderate vascular changes. It would therefore appear more likely that the recent severe haemorrhagic changes in the kidney were responsible for impairment of function. In addition, the effects of gastro-intestinal haemorrhage would play a part in producing azotaemia (Black, 1942). The haemorrhagic state in our patient, therefore, was probably the cause rather than the result of the uraemia.

Discussion

The pathogenesis of sulphonamide purpura is a subject for conjecture. The drug is sometimes directly toxic to the bone-marrow. The structure of the sulphonamide drugs is similar to that of benzol derivatives having a known myelotoxic action. The occurrence of agranulocytosis and aplastic anaemia during sulphonamide medication is well known. In such cases thrombopenia associated with the aplastic anaemia (Meyer and Perlmutter, 1942) and the agranulocytosis (Dolgopol and Hobart, 1939) has been recorded. However, the red and white cell elements are usually well maintained in the peripheral blood in the acute purpuras associated with sulphonamide therapy, the former showing only a slight fall consequent upon haemorrhage, and the latter often being raised. Bone-marrow studies in our case revealed abundant megakaryocytes and increased cellularity, particularly of the myeloid elements. Similar findings have been reported (Markel and Rike, 1939; Russell and Page, 1940; Losada and Fernandez, 1942; Gorham *et al.*, 1943). More probably the purpura results from a generalized vascular defect.

In recent years the importance of the capillaries in the pathogenesis of purpura has been stressed (Mackay, 1931; Macfarlane, 1941; Scarborough, 1943). In all the 7 recorded cases of purpura following sulphonamide therapy in which the resistance of the capillaries was tested a marked fragility was noted. In 9 out of 12 cases the bleeding time was prolonged. In 4 of the reported cases, including our own, the platelet count, although low, had not been reduced to the level usually associated with bleeding in essential thrombocytopenic purpura. Scarborough in a recent personal communication mentioned a case of thrombocytopenic purpura following the local application of sulphathiazole ointment in which, after recovery from the acute phase, and when the platelet level was restored to normal, application of sulphonamide drugs to the skin led to a marked fall in capillary resistance in parts remote from the site of application. There was no significant change in the platelet count. The effect on the vessels may be due to hypersensitivity. If drugs are administered in two courses hypersensitive phenomena are more likely to occur. In our case

the drug was given for 7 days; then a 5-day interval was allowed to elapse before restarting it. It was only on the second occasion that the supposed intolerance became apparent. The only other instances of spaced dosage associated with purpura are recorded by Russell and Page (1940), Harries (1942), Werner (1942), Gorham *et al.* (1943), and Hurd and Jacox (1943). In 8 cases the administration was uninterrupted. Drug hypersensitivity may remain after recovery. Hurd and Jacox found that giving a small dose of sulphathiazole or sulphadiazine to their patient caused a marked fall in the platelet count with an increased bleeding time and a positive tourniquet test. Rosenfeld and Feldman (1942), however, were able to give a later course to their patient with no further purpura.

In the reported cases no member of the sulphonamide group of drugs seems exempt as a causative agent, and sulphanilamide, sulphapyridine, sulphathiazole, and sulphadiazine have all been held responsible.

The high mortality of this condition—8 out of 9 cases proved fatal—makes early recognition essential. The first clinical sign is nearly always epistaxis. If this or other spontaneous bleeding is discovered in a patient receiving sulphonamide drugs the administration should be stopped immediately and a bleeding time and capillary resistance test done. Adequate transfusion of fresh blood is probably the best line of treatment.

Summary

A fatal case of acute purpura occurring in the course of sulphapyridine therapy in pneumonia is recorded.

The pathogenesis of this condition is discussed. Vascular lesions as a basis for its causation are emphasized.

In view of its high mortality a watch for extraneous bleeding should be made in all cases receiving sulphonamide drugs.

We wish to express our thanks to Prof. J. H. Dible and Dr. J. McMichael for much helpful criticism. The necropsy findings are reported by kind permission of Dr. C. Keith Simpson.

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HAEMOGLOBIN LEVELS IN THE WOMEN'S AUXILIARY AIR FORCE

BY

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Between May, 1943, and April, 1944, a survey of haemoglobin levels among various groups of W.A.A.F. personnel was carried out. The main purpose of the survey was to determine whether the average haemoglobin levels showed any significant change during service in the W.A.A.F. In addition some of the results have been incorporated into the report of the nation-wide survey of haemoglobin levels initiated by the Haemoglobin Survey Committee of the Medical Research Council, whose report will shortly be published.

Plan of Experiment

The following groups were chosen: (1) W.A.A.F. personnel arriving to join the Service in May and June, 1943. (2) W.A.A.F. personnel attending an N.C.O.s' course in June, 1943. (3) W.A.A.F. personnel at a bomber station and a training wing in Sept., 1943. At each station all the personnel were asked to volunteer for the test, and, except at the training wing, almost all volunteered.

The girls completed a card giving information required by the Haemoglobin Survey Committee of the Medical Research Council (see Appendix). The haemoglobin level was then determined on a sample of blood from the ear, using the technique suggested by the Committee and a standardized Haldane haemoglobinometer.

Results

Most of the W.A.A.F. were between 18 and 25 years of age and all between 18 and 35. The distribution of the haemoglobin levels in the groups of W.A.A.F. examined is given in the accompanying Table according to length of service. Separate analysis of the results for the N.C.O.s and the W.A.A.F. personnel from the bomber station and training wing shows no significant difference, so these groups have been combined.

It is seen that all the groups who had been in the Service for more than six months had significantly higher haemoglobin levels than the group of W.A.A.F. just entering the Service, but that after six months to a year there is no further improvement. The coefficient of variation, however, becomes steadily smaller with longer service. The mean value for all those who had been in the Service for more than six months is 103.05, with standard deviation 9.12. The results have also been analysed according to trade. Some of the trades are represented by very few W.A.A.F., so that comparison has been possible only for a few. There is no significant difference between the results for cooks and butchers, motor transport drivers, clerks, aircraft hands (general duty), and telephone operators.* Analysis of the results according to age shows no significant differences in the age groups represented (18–35 years).

Table showing Distribution of Haemoglobin Levels of W.A.A.F. according to Length of Service

Hb %	On Entry	Length of Service				
		½–1 Yr.	1–2 Yrs.	2–3 Yrs.	More than 3 Yrs.	Total More than 6 Mths.
126–	—	1	2	—	—	3
121–	—	1	2	1	—	4
116–	6	2	9	6	1	18
111–	6	5	9	16	2	32
106–	41	8	18	22	5	53
101–	80	10	26	25	5	66
96–	118	4	25	32	3	64
91–	143	14	12	15	7	48
86–	87	2	3	7	0	12
81–	52	0	1	2	1	4
76–	10	1	0	1	—	2
71–	8	—	0	—	—	0
66–	3	—	0	—	—	0
61–	2	—	1	—	—	1
56–	0	—	—	—	—	—
51–	2	—	—	—	—	—
46–	0	—	—	—	—	—
41–	1	—	—	—	—	—
Total ..	559	48	108	127	24	307
Mean value % ..	94·84	102·46	104·10	102·71	101·62	103·05
Standard deviation	9·22	9·90	9·51	8·47	8·26	9·12
Coeff. of variation	9·72	9·66	9·14	8·25	8·13	8·85

Forty of the W.A.A.F. from Group 1 were retested after ten months' service. The mean value of the haemoglobin levels of these girls on entry was 98.8 (standard deviation 8.32); after ten months the mean improvement was 4.25. This improvement is statistically significant (4.25 ± 1.70). The level reached is similar to that in the other groups with more than six months' service.

Discussion

Choice of Groups.—Almost all the girls in each group volunteered, so that there was practically no selection within the groups. The group of N.C.O.s were drawn from many stations to attend the course, and so constituted a fairly random sample of W.A.A.F. population so far as location is concerned. On the other hand, they were all training as N.C.O.s and were to that extent selected. They were presumably of more than average intelligence and their period of service was comparatively long; there was probably also some slight selection by trade. The group of W.A.A.F. from the bomber station and training wing, however, although selected as to location, were not selected by rank or trade. As the results for this group are not significantly different from those for the N.C.O.s,

* A smaller survey carried out on 82 W.A.A.F. aircraft fitters and 59 W.A.A.F. electricians showed the mean Hb of these to be 106.92 (standard deviation 10.2) and 106.87 (standard deviation 9.1) respectively. These figures are significantly higher than the mean for the general W.A.A.F. population after more than six months' service (difference 3.82 ± 0.91).

it appears that the selection in the two groups did not affect the accuracy of the estimate of mean haemoglobin levels. It is possible that the group of W.A.A.F. which entered the Service some time ago might be differently constituted as regards social status, etc., from those which were entering later. The results for the new entrants are, however, similar to those of other groups of the population (M.R.C. report, 1944), and it seems very unlikely that earlier entrants could have had haemoglobin levels so much higher. Furthermore, the haemoglobin levels of the 40 girls of this group retested after ten months were by that time similar to those of other groups of more than six months' service.

Accuracy of Results.—Errors in the estimation of haemoglobin by the method used in this survey arise from three sources: inaccuracies in the apparatus, errors in collecting the sample of blood, and the error in matching. The apparatus was standardized and the appropriate correction applied to all readings. These corrected values are those given in the Table. The error in collection has been estimated by collecting samples from the ear and vein of 25 subjects and measuring the haemoglobin level in the usual way. This test showed that the samples from the ear were approximately 4.2% higher than those from the vein. It is probable that the levels as estimated from venous blood are more accurate. The error in matching was assessed by a test instituted by the Haemoglobin Survey Committee. The full results of this test are published in the report of the Committee; it may be stated, however, that I tended to read too low, as did most of the others taking part. The average correction to be applied in the ten samples estimated was approximately +4.4%. It is probable that a similar correction may be applied to all the results given in this report. The errors in collection and matching are similar in size but tend to alter the true values in opposite directions, so that the results given in the Table may be taken as being about the true values. The retesting of the 40 girls in Group 1 was carried out after the results of the matching test had been made known, and it was possible, therefore, that this error was being unconsciously corrected at the second test. A further 194 girls who had just come into the Service were therefore tested. The mean haemoglobin value of this group was 96.15 (standard deviation 10.0), which is not significantly different from that of the girls in Group 1 (difference 1.31 ± 0.817). It appears likely, then, that the error in matching was not being corrected and that the improvement in the 40 girls was real.

Normal Haemoglobin Values.—The mean haemoglobin level reached after six months' service is higher than any of the levels usually regarded as normal. The figure given by Price-Jones (1931) is 98.3%, and this has usually been accepted as the best estimate of normal averages. On the other hand, the value reached by the W.A.A.F. after six months' service (103% approximately) is well maintained without further improvement. This would suggest that the normal value is at least as high as this. It is possible that some of the W.A.A.F. with low values might not be consuming much of the Service diet and might be capable of showing further improvement; this would tend to make the mean value even higher.

Cause of Improvement.—The improvement is probably largely due to the high iron intake of women in the Service. The average intake per person per day is about 35 mg. (see Macrae, 1944); much of this iron comes from iron cooking vessels, which are rarely used in domestic cookery. What part is played by the intake of much protein of high biological value is not known, but there is little evidence of deficient intake of protein in the general population (H.M.S.O., 1944). It is doubtful if vitamin C intake plays any part in the improvement. The average ascorbic acid intake of W.A.A.F. personnel is about 25 mg. a day in the autumn and about 18 mg. a day in the spring (Macrae, 1944). It is probably at least as high among civilians, because domestic cooking methods are on the whole less destructive of this vitamin. Some slight improvement in average values may be due to the medical treatment of a few W.A.A.F. with low haemoglobin who develop symptoms during Service life.

Summary

The haemoglobin levels of W.A.A.F. personnel entering the service is about 95% (standard deviation 9.22) on the standard Haldane scale. The haemoglobin level after six months' service is about 103% (standard deviation 9.12). This level is reached in six months to a year and is maintained thereafter. The error in collection results in readings which average approximately 4.2% too high, and errors in matching in readings which average approximately 4.4% too low. Correction for both these errors thus leaves the readings as given in the Table. It is probable that the "normal" mean value of women of this age group is at least 103%.

The improvement is probably due mainly to the high iron intake of W.A.A.F. personnel.

I am indebted to the commanding officers and W.A.A.F. administrative officers of the stations concerned and the W.A.A.F. personnel who took part in the test for their co-operation; to Dr. Bradford Hill for advice concerning the plan of the experiment and in the analyses of the results; and to Dr. Davies, pathologist to the Royal Gloucester Infirmary, for granting me laboratory facilities during May and June, 1943.

APPENDIX

Copy of Proforma Used in R.A.F. Haemoglobin Survey

Serial No.....

Name..... No..... Age last birthday.....

Date of joining W.A.A.F..... Married, Single, Widow.....

Home address.....

Previous occupation and town of work.....

Occupation of husband.....

Mark with a cross the circumstances applicable before joining the W.A.A.F.

a. Lived with family on civilian rations usually supplemented by regular meals (5 or more a week) at canteen or restaurant.....

b. Lived with family on civilian rations usually supplemented by some meals (less than 5 a week) at canteen or restaurant.....

c. Lived with family on civilian rations without supplementary meals as described or with some meals as follows (Give short description) .....

.....

d. Lived in hostel, institution, or other communal life as follows (Give short description) .....

e. Other circumstances as follows (Give short description) .....

.....

Serious illnesses during past six months ("Serious illness" if confined to bed for a week or more).....

Were you a blood donor?..... No. of donations in past 2 years.....

Date of last donation.....

No. of previous pregnancies.....Date of end of last.....

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Medical Memoranda

A Note on Red Hair, Rheumatism, Tuberculosis, and Bleeding

The question of rheumatism, red hair, and bleeding has been raised again in the *Journal* (July 1, 1944, p. 33), and the stimulating reply there given suggests that the following data are worth stating.

RED HAIR

Of late all patients with red hair who consulted me have been noted, and this report concerns 100 consecutive red-haired patients. The accompanying Table shows the conditions in which the red-haired were seen with any frequency. It is clear that only a small minority (6%) of patients with rheumatic fever had red hair. The 3% of pneumonia patients with red hair probably coincides with the incidence of red hair in the population dealt with. Hill and Allan (1929) found an incidence of 3.1% in London children. A larger series will be necessary before it can be affirmed that the incidence of red hair in rheumatic patients is substantially greater than that in pneumonia or in the general population.

Hill and Allan (1929) found that 6.4% of 562 rheumatic cases had red hair, but only 3.1% of 536 controls (percentages which I confirm). According to the contributor in the *Journal*, this difference in 500 patients is probably significant. Yet Hill and Allan concluded that there were no physical characteristics peculiar to rheumatic children, no doubt because they considered other colours of hair and also eye colour, and did not concentrate on red hair alone. Shrubsall (1903) found that blond traits were associated with acute rheumatism and tonsillitis, and brunette traits with pulmonary tuberculosis and malignant disease. Yet pulmonary tuberculosis was the chief disease with red-haired sufferers among these 100 red-haired

But in conformity with Shrubsall I saw malignant disease in 2 red-haired patients only. It should be of value further to study the incidence of red hair in pulmonary tuberculosis, rheumatic fever, acute tonsillitis, purpura simplex, and epilepsy.

BLEEDING

The contributor to the *Journal* stated that he had no knowledge of any work on red hair and excessive bleeding. There is, however, evidence that rheumatic fever is associated with unusual (if not excessive) tendency to bleed. The tendency of rheumatic persons to nose-bleeding is discussed by Levine, Andren, and Homans (1930). Coburn (1933) found post-mortem evidence that rheumatic fever was associated with diffuse haemorrhagic changes. I (Davis, 1941, 1943) have given evidence of a special association between purpura simplex and rheumatism. I do not yet know whether this association is stronger in red-haired rheumatic subjects. Although many clinicians will have seen purpura in tuberculosis the association is relatively rare (Davis, 1943). It might also be worth while investigating this association in red-haired tuberculous patients.

Details of a Series of 100 Red-haired Patients (Diseases in which Red Hair was seen in more than 3 Patients)

Disease	Total Cases	Cases with Red Hair	Percentage of 100 Red-haired Patients
Pulmonary tuberculosis	296	23 (7·8%)	23
Rheumatic fever (past or present)	248	15 (6·0%)	15
Acute tonsillitis	162	12 (7·4%)	12
Pneumonia	270	8 (3·0%)	8
Purpura simplex	59	7 (12·0%)	7
Epilepsy	47	6 (13·0%)	6

COMMENT

Of 240 patients with rheumatic fever 6% had red hair, as against 3% of pneumonia patients and 7.8% of sufferers from pulmonary tuberculosis. Of a series of 100 red-haired patients, 15% were rheumatic, 23% were tuberculous, and 12% had acute tonsillitis. There is a special association between rheumatism and purpura.

I thank Mr. J. R. M. Whigham, F.R.C.S., and the staff of St. Andrew's Hospital for their help.

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Intussusception after Appendicectomy

The following case is recorded as a rare instance of intestinal obstruction after operation.

An otherwise healthy boy was admitted on June 22, 1944, suffering from abdominal pain and vomiting of 12 hours' duration. His temperature was 99.8° and pulse 120, and he was tender in the right iliac fossa. The same day I removed his appendix, which was long and inflamed. Nothing else appeared wrong, though in view of the pathological appendix I did not make a search. His temperature fell to 98.4° the next day. He was happy, free from pain, ate his meals, had his bowels open, and was apparently convalescent.

On June 29—the seventh day after operation—his condition changed. His appetite went and he was fretful, but he did not complain of any sudden or serious abdominal pain. His bowels were open for the last time on that evening. The next day he began vomiting, he had absolute constipation to enemas, and his abdomen was tender to palpation. The wound was well healed. I did not think I could feel any definite abdominal mass. Some mucus was passed per rectum, but no blood.

On July 1 his abdomen was distended and there was visible peristalsis. I opened the abdomen again, and found a large, fairly tight enteric intussusception in the ileum, about a foot from the ileo-caecal valve. With a little difficulty it was reduced. The gut was viable. There was no Meckel's diverticulum. The next day his condition was excellent. He was happy again, began taking light diet, and his bowels were opened regularly. His convalescence since then has been uneventful.

The question arises: Could he have had the intussusception when I removed his appendix on June 22, or was it initiated by the abdominal manipulations? It was reducible and viable nine days after the initial operation.

I wish to thank Dr. Geoffrey Dudley for permission to report this case.

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Reviews

PHYSIOLOGY OF THE C.N.S.

Physiology of the Nervous System. By J. F. Fulton, M.D., Sterling Professor of Physiology, Yale University; formerly Fellow of Magdalen College, Oxford. Second edition. (Pp. 614. 38s.) London: Oxford University Press.

The appearance of the first edition of this book in 1938 marked an important phase in the current intensive study of the central nervous system, and was a most welcome addition to physiological literature. The second edition puts us still further in Prof. Fulton's debt, by bringing the subject well up to date, and introducing further improvements in the display of facts and figures.

Some of the chapters have been largely rewritten, and particular stress has been laid on the biochemical aspects of the subject, such as the significance of acetyl choline in relation to nerve transmission, and on the important developments of the method of following nerve impulses by recording the electrical variations from point to point. Important results of developmental research are incorporated, and also advances in our knowledge of cutaneous receptors, of the functions of the basal ganglia and parietal lobes. There is a chapter on conditioned reflexes by Dr. H. S. Liddell, which gives an account of interesting work on sheep, and in general somewhat modifies the point of view taken by the Pavlov school.

A remarkable feature of the book is the splendid bibliography: one would expect a good list of references from Prof. Fulton, but this one is quite exceptionally valuable. The general get-up of the volume is excellent.

HEALTH SERVICES

The Nation's Health. By Prof. J. M. Mackintosh. Target for Tomorrow No. V. (Pp. 64; illustrated. 4s. 6d.) London: The Pilot Press.

A series of books under the general title of *Target for Tomorrow* is being published under the supervision of Sir William Beveridge, Dr. Julian Huxley, and Sir John Boyd Orr. The fifth volume in this series, by Prof. James Mackintosh, in 64 profusely illustrated pages, tells the general reader a good deal of the story and breathes the spirit of a reformer more interested, perhaps, in the wider problems of the public health than in those that beset the private individual when he seeks the advice of his family doctor.

The very short chapters are successively entitled: "Health: the Problem"; "Doctor: Patient and Health Insurance"; "Hospital, Consultant and Nursing Services"; "Maternity and Child Welfare"; "Other Health Services"; "The Problem of Health Administration"; "Medical Research"; "In Other Countries"; "Health: Plans and Opinions"; "A Target for National Health." The short text is pithy and informative, and the author has evidently relied on photographs to fill in the gaps he has left. It is not always clear why he has chosen the pictures he has: for example, in the 4½ pages given to "Hospital, Consultant and Nursing Services," 2½ are occupied by reproductions of Florence Nightingale in the military hospital at Scutari, Lister in a King's College Hospital in 1893 (in a charmingly old-fashioned group), and of one of the latest and brightest wards in "an up-to-date public hospital run by the London County Council." A lay person will no doubt say to himself, "The public hospital has it." But the comparison, if a comparison is intended, is unfair. To give one whole page to a photograph of a small boy cleaning his teeth does not really throw much light on the dental services of the country or on the problem of dental caries, and to give 4½ pages to illustrating the Peckham Health Centre seems a little out of balance in a book of this size. On the other hand, a full-page view of an occupied bedroom in West Ham says more about the evils of overcrowding than any number of tables, charts, or verbal description: this picture tells a story and drives it straight home.

The author may have been writing against time, and his book was already drafted when the Government issued its White Paper in 1944: he must be congratulated on the skill with which he met this awkward situation and on the excellent and concise summary he gives of the Paper. But we doubt whether members of the

public health service, of which he is a distinguished representative, would agree with him that the White Paper provides a solution for the "confusion in local health administration." It may, however, provide a solution for the "duality of the voluntary and public hospitals," but the solution is one that disturbs those who still cling to the idea that the voluntary hospitals of this country represent something that is of profound significance in our communal life. Prof. Mackintosh, discussing the organization of professional and hospital services, refers to the "obstinate traditions and habits of thought" of "these institutions": it appears—though this is not quite clear—that he refers to hospitals. Does this adjective "obstinate" reflect the ambitions of the reformer who sees little virtue in the continuity of history, and looks upon tradition as an obstacle and not as a guide? At all events, he seems to dispose quite easily of the tradition of freedom when he says of the Medical Appointments Committee which he believes should control the distribution of doctors, "they should be able, in addition, to divert medical men to areas where the number of doctors is insufficient."

In a last short note under the heading "Experiment and Research" he writes: "The Medical Research Council should continue to supervise this all-important side of the forward drive towards the health target, but under the general direction of the central health authority." Does Prof. Mackintosh suggest that the work of the Medical Research Council should come under the control of the Ministry of Health? We may recall that on the creation of the Ministry of Health in 1919 the direction of the M.R.C. was transferred to a Committee of the Privy Council when it ceased to be the Medical Research Committee established to administer the money for medical research provided by funds under the National Insurance Act. The secretary of the M.R.C. is also secretary of the Privy Council Committee for Medical Research, and this and the method of appointment to the M.R.C. safeguard it from too much State interference. We think Prof. Mackintosh's proposal would push the clock back, not on.

In a couple of pages the author describes with admirable brevity some points in the health services of the U.S.A., the U.S.S.R., and Sweden. Describing what happens in the U.S.S.R., he writes: "Under the Soviet Constitution citizens are guaranteed the right to medical treatment at the expense of the State, and they also receive maintenance in the event of loss of working capacity through illness. This general principle has made it possible to build up a comprehensive medical service at the expense of the State, which pays and employs all medical and auxiliary workers." No doubt this is the only way a comprehensive medical service can be built up under the Soviet Constitution, but we believe that it is possible to reach the same goal by different means under the British Constitution. Yet this short description of what is now done in Russia might almost be used to describe what the Government is proposing should be done in Great Britain.

MEDICAL PARASITOLOGY

Medical Parasitology. By James T. Culbertson. (Pp. 285. $4.25 or 28s.) New York: Columbia University Press; London: Oxford University Press.

This book does not claim to be a complete treatise on medical parasitology. It has been written for medical men and medical students who have in no way specialized in tropical medicine and who in the future will require to know the fundamentals of the subject, since the intermingling of populations owing to the war and the increased facilities for travel will break down many of the barriers which have separated tropical from temperate diseases. It is increasingly realized that the sharp demarcation between the temperate and tropical countries no longer exists, and that many of the parasites and the diseases they produce which were regarded as peculiarly tropical will to an increasing extent be world-wide in their distribution. Accordingly the author has written this book primarily for medical men whose sphere of work is outside the Tropics. There is no lengthy description of the structure or development of the parasites, but enough information is given to make intelligible what is said under the headings of pathogenicity, immunity, diagnosis, specific therapy, and prophylaxis. The illustrations are simple and adequate, though in some cases possibly a little sketchy. All the disease-producing protozoa and helminths are considered, as also the Arthropoda of medical importance. There is a useful appendix of the more important technical methods employed for the detection and examination of the various parasites; also an introductory section giving general consideration to the subjects of infection, epidemiology, natural and acquired immunity, diagnosis, specific therapy, and prophylaxis.

The book is undoubtedly a useful one, and more particularly so for those who are taking up the study of human parasitology for the first time.

THE BILIARY SYSTEM

Clinical Lectures on the Gallbladder and Bile Ducts. By Samuel Weiss, M.D., F.A.C.P. (Pp. 504; illustrated. $5.50 or £1 14s. 6d.) Chicago: Year Book Publishers, Inc.; London: H. K. Lewis and Co.

This book presents an account of the anatomy, physiology, and diseases of the biliary system from the physician's point of view, together with the appropriate methods of examination and investigation. Surgical technique is completely excluded. The material is obtained in part from the author's experience, but even more from the literature, and it tends to fall between the two stools of the personal investigation and the full-scale review. The title "Clinical Lectures" is unfortunate in so far as it invites comparison with vivid writers such as Trousseau and Hutchison. The main faults of Dr. Weiss's book are that it is dull reading and that the reader is often given no guiding thread to find his way through the contradictory opinions that are quoted. The chapter on liver function tests, for example, has no broad discussion of the tests, no hint of the theories on which investigators have worked, no summing-up of the relative value of the tests, but merely a sequence of tests arranged without rhyme or reason. Neither pernicious anaemia nor acholuric jaundice is mentioned in the index or in the text, though both diseases are often complicated by gall-stones. The book will be most useful to the physician preparing to give a lecture or present a case of biliary disease. It is too undigested for the student. It is well produced, with good illustrations, though it is a little difficult to see why a kneeling Venus should have been chosen as the model for surface markings and reflex disturbances; she is certainly not the gall-bladder type.

Notes on Books

Volume XII (1943) of the *Brompton Hospital Reports* (price 8s. 7d. post free from the Secretary of the hospital) contains 13 papers by members of the staff. Only two of these papers have not previously been published. Six articles deal with various aspects of tuberculosis. Mr. Price Thomas and Dr. Cleland discuss exhaustively, with excellent illustrations, the indications, technique, and complications of extrafascial apicolysis with thoracoplasty. In another paper, on the results of thoracoplasty, they show that the death rates have been materially reduced as increased experience has been gained in selecting cases and in operative technique; and that more expensive operations, employing mobilization, increase the prospects of cavity closure and sputum conversion, but they do not increase the mortality or risk of complications. In the paper prepared by Dr. A. Margaret C. Macpherson—"Childhood Infection and its Relation to Adolescent and Adult Pulmonary Tuberculosis: A Record of the Work of the Brompton Hospital Research Department during the last 14 Years"—it is stated that a shallow pneumothorax with only a short stay in hospital is the correct form of treatment for "symptomless adolescent pulmonary tuberculosis." Many tuberculosis workers will disagree with this. Among the articles dealing with subjects other than tuberculosis, attention should be drawn to the painstaking work of Dr. Foster-Carter on the anatomy of the bronchi; and all members of the medical profession will be interested in Dr. Hope Gosse's survey, "The Health of the Doctor." The volume also contains the hospital's medical reports for the years 1939–42, and an index of authors and a general index of Volumes I to XII.

In *Cape Horn Sunsets* (Mellifont Press Ltd.; 1s.) Dr. M. F. MCELLIGOTT describes his experiences as a ship surgeon on a voyage to Australia, outward round the Cape of Good Hope and homeward round Cape Horn. The book is chiefly written in the form of a somewhat discursive diary, whose pages are freely sprinkled with the author's reflections and reminiscences.

BRITISH MEDICAL JOURNAL

LONDON

SATURDAY SEPTEMBER 23 1944

VESALIUS THE MAN

The *De humani corporis Fabrica* of Vesalius, first printed at Basle in 1543, is the greatest single contribution to the medical sciences. Moreover it ranks among the most beautiful books of the sixteenth century with an assured place in the annals of draughtsmanship and of the wood-cutter's art. Its plan and execution, with those of its companion the *Epitome*, were completed within the astonishingly brief space of three and a half years. Its author was then but twenty-eight. Nought else by him is of even secondary scientific value. Without these twin books his career would be of little interest. Despite much research we have only meagre details of his life. The late Prof. Roth of Basle spent many years seeking details of his career, for which Roth's monograph of 1892 is still our chief source. It is a model of exact statement but quite fails to yield the picture of a personality. Beyond a few references in contemporary sources and half a dozen rather improbable traditional stories we have only Vesalius's own writings in which to discern him. For such reasons his other works are worth close examination.

Harvey Cushing applied himself during some forty years to the task of eliciting a picture of the real Vesalius from his writings and from direct and indirect references to them. He left his book about half finished. It exhibits extraordinary bibliographic skill and patience, and has been prepared for publication by Prof. Fulton, assisted by Dr. W. W. Francis.[1] Their modest reticence prevents us, as they would wish, from ascribing an exact share to either. In effect something like a quarter of their beautiful volume must be regarded as a pious memorial by these two scholars to their late colleague. Bibliography does not lend itself to detailed criticism. The proof lies in the use thereof. During several months we have referred repeatedly to this book, and testify to its completeness, convenience, and reliability. We discuss some of its information, treating the works of Vesalius in chronological order.

I. His first publication was a paraphrase of a Latin translation of part of a book by the well-known Arabic writer Rhazes, printed at Louvain in 1537. It may be regarded as a graduation thesis. In it we can ourselves discern neither originality nor promise nor deep scholarship. There is some evidence that it was mainly copied from a document in the possession of his family. That it appeared six times in its own century only proves once again that mediaeval medicine died hard. Perhaps it is not quite dead yet.

II. The *Tabulae sex*, printed at Venice in 1538, is a group of large anatomical sheets, three of the heart, great vessels, and generative organs drawn by Vesalius himself, and three of the skeleton drawn by the artist Calcar. Those by Vesalius are highly traditional. We believe the figures of the heart and vessels to be based on animal anatomy and probably on that of a rhesus monkey. Those by Calcar are drawn direct from the skeleton of a youth of 18 articulated by Vesalius. They are a real advance on representations of the kind. All six plates have a running text that is at once a monument and a curiosity of anatomical nomenclature. To this text Cushing unfortunately gave no attention. The *Tabulae* were immediately copied by plagiarists. To them, on the other hand, Cushing gave more of his time and skill than their interest seems to us to warrant. He demonstrated, however, that the scheme spread very rapidly in German lands. Base imitations took the place of the original, which was not reprinted. Perhaps it was too large for convenient transit and too expensive for slender purses. Only two copies survive. The original figures were used for class demonstration. Vesalius added a drawing of the cranial nerves which has disappeared but is substantially represented in the *Fabrica*.

III. *The Institutes of Anatomy according to the opinion of Galen, for Students in Medicine, by Johannes Guenther of Andernach, edited, amplified and corrected by Vesalius*; Basle, 1538.—Guenther (1505–74) was a good Greek scholar whose laborious life was largely spent in making over-hasty translations of works of Galen into Latin. He came to Paris in 1527. Some six years later Vesalius began to study under him. The master had a deep influence on his pupil. We could wish that he had transmitted his own clear manner of writing. Guenther's *Institutiones anatomicae* was what we would now call a "cram-book." It appeared first at Basle in 1536, and contains a statement that the promising young Vesalius had demonstrated "for the first time" that the "origins" of the spermatic veins differ from those of the arteries and also from each other on the two sides. It has perhaps not hitherto been noticed that this fact had been recorded at Bologna, the leading Italian school till Vesalius, by Mondino da Luzzi in 1316 and by Giacopo Berengario da Carpi in 1523. The works of both had been reprinted several times by 1536. That Guenther had not heard of this point illustrates, what we know well on other grounds, that the Parisian medical school was almost completely isolated from the Italian schools. Vesalius revised this work of Guenther at the same time as the *Tabulae sex* was issued. "What may have led Vesalius to edit a new edition of Guenther's compendium is not apparent," writes Cushing. We suggest that he regarded it as the best available companion to the *Tabulae*. It would be worth collating the edition revised by Vesalius with the original to see how the changes fit the *Tabulae*.

IV. The *Venesection Epistle*—Basle, 1539—is a member of a long, fierce, and futile controversy as to which side to bleed in pleurisy. Vesalius based his view on the course of the azygos vein and its tributaries and accessories. These we now know to be highly variable. In any event they are irrelevant to such treatment.

V. Contributions to the *Opera* of Galen.—Renaissance appetite for ancient medical literature was insatiable. Its *bonne bouche* was a set of huge tomes of the works of Galen. Some twenty editions appeared in the sixteenth century. The most prized were those of the Venetian firm of Giunta. From 1541 onward they included three works revised by Vesalius. The largest was *De anatomicis administrationibus*, of which only about half was then known. Rendered into Latin by Guenther and printed at Paris in 1531 and several times since, it formed the staple text for more advanced students at Paris. In revising it Vesalius was on very familiar ground, as he was for the two small tracts which he revised for the same volume. A collation of these three revisions with their originals is necessary before any clear verdict can be given on the Greek scholarship of Vesalius. Indications suggest to us that it was quite superficial.

VI and VII. The *Fabrica* and its companion the *Epitome* must form the main theme of every account of Vesalius. To these works we devoted a leading article on their centenary last year (see our issue of June 26, 1943). It is a puzzle why Vesalius, working at Padua and often visiting Venice, the great neighbouring printing centre, should risk woodblocks and MSS. by sending them across the Alps on a journey of

[1] *A Bio-Bibliography of Andreas Vesalius*. By Harvey Cushing. Schuman's New York, 1943; $15.00.

350 miles, to have his work printed at Basle. We suggest that Basle, being on the Rhine, was convenient for distributing such very heavy books. They could go by water to the north and west of Europe and notably to Germanic lands, where Vesalius wished specially to be read. A German translation of the *Epitome* was in fact made under his own eyes at Basle. Its circumstances have been examined by Prof. Sigerist.[2] Much has been written on the famous title-page of *Fabrica* and *Epitome*. Cushing exhibits the alleged first, second, and third stages of this remarkable work of art. We confess scepticism as to their genuineness. On the other hand, there can be no doubt that the background of the famous muscle figures has been identified as a landscape near Padua. It must have been drawn on a panoramic scale and the figures afterwards filled in. By studying watermarks Cushing proves that at least one copy survives of a second edition of the *Epitome* printed in 1555 from the same blocks as the first.

VIII. The *Epistle on China-Root*—Basle, 1546—is scientifically the least worthy of the Vesalian works. Its medical outlook is not above that of the day, and is far below that of its greater contemporary exponents, such as Fernel. It reveals, however, some personal relations of Vesalius. For this reason Cushing rightly investigates it thoroughly.

IX. There survive a few *Consilia* of Vesalius. These are replies to questions from professional colleagues concerning specific cases—a conventional literary form of the day. One or two disclose surgical acumen. We could hardly expect less.

X. Second (folio) edition of the *Fabrica*—Basle, 1555, with some not very important improvements on the first edition.

XI. A long *Letter to Fallopius*, printed in 1564 in reply to legitimate criticisms of the *Fabrica*. It weakly stresses verbal rather than real points of difference. Perhaps it was not written for publication.

This is a very poor output for a life centred round the glorious *Fabrica* and *Epitome*. Except for them nothing by Vesalius would be any loss to science. There is the problem. Why was the unique genius of the man fertile only for three or four years? How came it that the greatest exponent of science of his century abandoned his career for a place at court? What sort of character can we descry through the fog of eulogy and legend and sheer hero-worship? To this enquiry, the background for which has been provided by Cushing, three solutions have recently been propounded.[3]

Dr. Ludwig Edelstein pictures Vesalius as embracing ardently the programme of the "humanist" party. To this he adhered in a deeper sense than in mere respect for classical antiquity. He was a humanist in holding certain aesthetic, historical, and philosophical views characteristic of that great movement and different from those of most of his contemporaries. The points are well made and we concur. But this aspect of Vesalius needs further annotation. First, the "humanist" language of the *Fabrica* is conspicuously unsuited to scientific discourse. Vanity led him to adopt a pseudo-classical style which is neither lucid nor succinct nor beautiful: a thoroughly bad linguistic choice. Secondly, a particular kind of humanism had given him a special bent. From 1531 to 1533, when he was between 17 and 19, he was at the "Collegium trilingue" at Louvain. This three-tongued college and its typical product the "trilinguis homo" had a meaning peculiar to its time and place. Erasmus (1467–1536), embodiment of the humanist spirit, when he coined the term meant one who had gained entry into the spirit of the Latin, Greek, and Hebrew literatures. The trilingual college at Louvain had been founded a few years earlier by a friend of Erasmus and of Sir Thomas More. Its distinctive ideal left its mark on the young Vesalius though already fading in the place of its birth. Most "humanists" of the day had come to live in a mental atmosphere composed almost entirely of language. Vesalius was far too great to be of these. His sympathies, we suggest, were with the Erasmian school, though he could never have become a trilinguis homo. But his exhibitionist temper led him to overstrain his equipment, so that we see him at once a poor ape of Cicero and a literary dandy flaunting spurious linguistic jewels. His boastfulness bewrayed and betrayed him.

Dr. Zilboorg, an eminent psychiatrist, has sought to display the inner mental life of Vesalius. He regards him as a split and withdrawn personality who, in the end, approached the border-line of insanity. Dr. Zilboorg's theory fits very well the scanty and uncertain data concerning the later years of the great man, but seems to us to fit ill what we know of his earlier years. For we cannot follow Dr. Zilboorg in distinguishing anything sadistic, and still less necrophilic, in the young Vesalius. His boyish interest in the insides of animals seems a healthy inquiry into living mechanism and structure, while his great work cries aloud that it is on *living* anatomy. Nor does Dr. Zilboorg's portrayal fit the well-known portrait of the cocksure, extroverted, sarcastic, vigorous little man that certainly represents the great Paduan teacher. But Dr. Zilboorg renders a service in stressing that, after leaving Padua, Vesalius really did undergo some profound mental change. It seems more likely to us that this took its rise in some intercurrent stress or intoxication. But his immediate reason for abandoning anatomy seems to us no mystery at all. In a worldly sense it was great promotion for a Paduan professor to become physician to the Emperor. No one has yet suggested that Vesalius was unworldly.

Lastly, in a highly erudite, provocative, and witty contribution, Mr. W. M. Ivins of the Metropolitan Museum of Art, New York, would solve the problem of Vesalius by treating him as a Renaissance Mrs. 'Arris. His figure, he suggests, has been created partly by the imagination of scholars and partly by the man's own success in appropriating the work of another. Between 1539 and 1542 "Vesalius according to his own account (1) made two trips to Bologna, where he performed a public anatomy, (2) began and finished editing three of Galen's texts, (3) read Avicenna with Lazarus Hebraeus and compared the text with Hebrew MSS., (4) wrote a careful paraphrase of all ten books of Rhazes, (5) collected the recipes of the classical authors, (6) conceived the ideas for a number of other books . . . (7) carried on his professional task of lecturing and dissecting, and . . . (8) began the text of the *Fabrica*, which he finished in August, 1542." In addition (9) he supervised the artist or artists in the preparation of the 280 woodcuts to the *Fabrica* and *Epitome*.

Since this achievement seems a miracle rather than a *tour de force* of genius, it is well to scrutinize Mr. Ivins's list. The editing of the texts of Galen (2) was a mere trifle involving a few days or perhaps hours. Vesalius surely had ample notes on them from his student days. Two are mere

[2] *Bulletin of the History of Medicine*, Vol. XIV. Baltimore, 1943.
[3] All three appear in the same number of the *Bulletin*.

short tracts. The reading of Avicenna in Hebrew (3) may be dismissed altogether. Vesalius, whatever he may suggest, was quite ignorant of both Hebrew and Arabic. He had hardly grasped even the phonetic value of the letters of these languages. There is no evidence that he ever approached the text of Rhazes (4) with any serious editorial intent. Neither collecting recipes (5) nor conceiving ideas (6) is a time-consuming process. Demonstrations (7) are to most professors what they care to make them. Before the days of preservatives anatomies could never be prolonged. In any event, they fitted the scheme of the *Fabrica*, as did (1) his two visits to Bologna, a short and easy journey. Lecturing (7) would be but trying out the text of the *Fabrica*. As for that text, its obscure and pretentious style is involved and repetitious to the last maddening degree. Easy writing makes hard reading, and the book shows many signs of haste. It might well have been compressed to a quarter of its bulk. It is certain that the greatness of the man was not in the written word. Vesalius is ungenerous and perhaps disingenuous in failing to mention his artist. It is usually assumed, on slender evidence, that Calcar was the man, but there are points against him and we are far from convinced. Mr. Ivins seems to overstress the difficulties of an anatomically untrained draughtsman in representing structural detail under skilled guidance. At the same time he underestimates the draughtsmanship of Vesalius himself, of which we have some means of judging. To Calcar Mr. Ivins gives most of the credit of the *Fabrica*. But of Calcar we know even less than of Vesalius.

> Seyde Plato, "Ye, sir, and is it thus?
> This is ignotum per ignotius."
> (Chaucer, *Canon Yeoman's Tale*, lines 1456–7.)

No, there was certainly a human and a very great Vesalius. He was clearly not a man of many friends. He had some repellent traits; in his later years he was secretive and eccentric and may even have been semi-insane. He was certainly vain and boastful, and as a writer had most of the faults of the humanists and few of their virtues. His worst feature perhaps came out in his ambition, for he abandoned, as have many, a great scientific career for the meanly reflected glamour of a life at court. But there is every reason to believe that he was, in every material sense, the creator of the *Fabrica* and the *Epitome*. He was therefore the greatest of modern medical men. But much more patient research is needed before we can discern clearly the essential elements of his character.

MEDICINE AND POLITICS

The present lull in medical politics will give many the much-needed opportunity to reflect upon events before the Annual Representative Meeting at the beginning of December. The Press generally, and the *Times* in particular, have given generous space to discussion on the numerous controversial points that have come to the fore since the publication of the White Paper. The political axe-grinders have tried to prejudice the issue by suggesting that opinions held by the medical profession and the B.M.A. have hardened into reactionary opposition. The medical profession has, indeed, reacted to the attacks made upon it, and to the misrepresentations made by those who want to use medicine to further their political aims. As Lord Dawson in his admirably phrased and wise letter in the *Times* of Sept. 16 observed, "There is a school of political thought desirous of seizing this opportunity for furthering its particular ideology of socialization, which would mean for medicine a whole-time service as part of the Civil Service and its members one and all paid by salary." Lord Dawson shows how fully aware he is of the activity of "extraneous forces" when he goes on to say: "The intent and impact of this influence, in the face of the Government's repeated assurance that they have no such intentions, *undermine confidence and render difficult the efforts of those on both sides who are seeking the way of agreement*" (our italics). And he lends force to his own observations by quoting the following from a recent speech by the Prime Minister: "Ideology too often presents itself as undue regimentation of ideas and may be very likely incompatible with freedom." These views have been consistently expressed by the *Journal* and reiterated in several leading articles over the past two years. Doctors up and down the country have become more and more disquieted by the attempt on the part of "ideologists" to exploit the situation created by the war with the aim of imposing their doctrinaire political conceptions upon a profession which is perhaps ill acquainted with the astuteness of political propagandists. That doctors have "reacted" to this situation is a welcome sign. It is, however, false to interpret this "reaction" either as a refusal to co-operate with the Government or as a sign of ignoring the need for medical reforms. As Lord Dawson points out once more, this is contrary to the facts. "There is," he states, "little dispute over objectives, but there are differences about methods of administration on which accommodation is being sought." He says flatly that "advisory committees standing alone outside the executive body are futile," and that "the profession insists on a substantial share in the planning and administration of the proposed service at every level." One thing this war has taught us, he acutely observes, is "that national enterprise must be guided by expert knowledge." "Can it be pretended," he asks, "that local authorities know anything about medicine?": and suggests a way out of this obvious dilemma by proposing that "medical and other skilled persons" should serve on local bodies alongside the elected representatives of the people. He emphasizes that the profession does not seek to dominate but to share the work of planning and execution. Turning to central administration, he asserts that the profession has no wish to wrest from the Minister and Parliament final responsibility for the proposed service, but he is equally clear that the profession "*will not accept subjugation by the service*" (our italics). The fear of doctors that civil servants want to be the "masters" and not the "obedient servants" is by no means groundless. Lord Dawson has put an unerring finger on the central weakness of the planner's anatomy.

SODI. BIC.

The dyspeptic is always with us, and sodium bicarbonate alone or in company is in many instances his sheet anchor. This drug, however, has fallen on evil days among the pharmacologists. The usual teaching is that after a brief period of neutralization hydrochloric acid appears in increased amount in the gastric juice. The mechanism underlying this "rebound" secretion has not been satisfactorily explained. Adams and his colleagues[1] mention the possibility that the increase in hydrochloric acid concentration may be due to more rapid emptying of the stomach, with consequent decrease in the dilution of the high acid secretion of the oxyntic cells. In an attempt to throw light on this problem they made use of the Cope gastric pouch in dogs and thus obtained an accessory stomach with nerve supply intact, and so situated as to act as its own collection vessel. The sole drawback to this technique was the necessity to use an antacid to prevent peptic ulceration: for this purpose measured amounts of aluminium hydroxide were employed with advantage. By this means it was possible to measure gastric secretion continuously. Control investigations showed that under constant conditions the day-to-day variations were very slight. The effect of sodium bicarbonate was determined by the intragastric administration of 50 c.cm. of 1.5 or 2% solution of sodium bicarbonate or by placing a 4% solution directly into the pouch. The 24-hour volume and total chloride were unchanged, but greater amounts appeared directly after the administration of the alkali. The secretion of free acid also showed an immediate increase which was only partly compensated by the later decrease, so that the amount secreted during the 24 hours was significantly higher than in the control period. The rebound increase in free acid which has been noted in the human subject is therefore in part due to a more rapid secretion produced by the bicarbonate, and the acid concentration is still further enhanced by more rapid emptying of the stomach. The actual mechanism producing these changes is still obscure, but the fact that the effects are the same whether alkali is put into the stomach or into the pouch suggests that it is more than a mere local effect on the secreting cells. If necessary this work confirms still further the view that continued administration of sodium bicarbonate is deleterious to patients with peptic ulceration, because for a long period after each ingestion of the alkali the ulcerated area is exposed to higher concentrations of free acid.

[1] *Amer. J. Physiol.*, 1943, **139**, 356.

CHAIR OF CHILD HEALTH IN LONDON

With Lord Nuffield's full approval the Trustees of the Nuffield Foundation have decided to allocate £10,000 per annum for a period of 10 years for a Chair of Child Health in the University of London. The offer of the Trustees has been gratefully accepted by the University. The financial assistance provided by the Foundation will enable a postgraduate Institute to be created for teaching and research on all aspects of child health. It is proposed that the Institute should be associated with the Hospital for Sick Children, Great Ormond Street, and the Obstetric Department of the British Postgraduate Medical School at the Hammersmith (L.C.C.) Hospital, London. Lord Nuffield and the Trustees of his Foundation believe that the promotion of child health must have a prominent place in the organization of the future health services of the country. They appreciate that the development of research and training in this sphere of health service requires new and enlarged facilities. The provision of academic centres for the teaching of child health is already being undertaken in several provincial universities, and the Nuffield Provincial Hospitals Trust has, within the last three years, made a substantial contribution to the University of Durham to assist in the creation of a Chair of Child Health at King's College, Newcastle-upon-Tyne. The munificent grant the Nuffield Foundation is now making has been influenced by the desire of the Trustees that the exceptional resources of the University of London for medical postgraduate education and research may be developed in a manner which will make the new Institute of Child Health worthy of the capital city of the country and the Empire.

BIOPSY IN SCHIZOPHRENIA

It is notoriously difficult to protect after death tissues removed from the body from post-mortem changes which complicate and obscure the histological picture. Furthermore, there will often have been changes during the terminal illness to add to the difficulties of interpretation. The pathologist is, in effect, forced to rely on his wide experience of control material, in the form of tissues believed to have been healthy, for a comparison on which to base his judgment. It might be thought that the whole difficulty could be evaded by the use of biopsy material. Tissues removed from the living body and fixed with great speed might be expected to be fairly free from these unwanted adventitious changes. There then arises, however, a second source of difficulty. The new method introduces cellular changes of its own, and the pathologist, as a rule, has by no means the same wealth of experience of control material to guide him. Bioptic examination of the brain is of much interest and value. For some purposes—e.g., studies on the oligodendroglia—it is essential, as agonal changes lead to swelling of these cells.[1] In neurosurgical practice biopsy investigations are of the greatest value in connexion with the treatment of tumours. Nevertheless the artefacts which can be produced in these small pieces of tissue, and which are then liable to misinterpretation as pathological findings, were well known to Nissl,[2] and have been made the subject of an experimental study by Rose.[3] Nissl's chronic change of cell sclerosis may be entirely due to the effects of fixation.

Kirschbaum and Heilbrunn[4] have recently reported an investigation by biopsy of the brains of schizophrenic patients and experimental animals. Fully aware of the dangers referred to, they took precautions by procuring animal controls. It is not clear that this control work was on an entirely adequate scale. Their human material was obtained from physically healthy schizophrenic patients during the operation of prefrontal lobotomy. The cases were chronic, with an average duration of illness of over fourteen years, so that the changes that might be looked for with a fresh and florid psychosis could not be expected. The authors found degenerative changes of the ganglion cells and progressive and regressive reactions of the glia and blood vessels, such as are commonly seen in cases of chronic intoxications and metabolic disorders. Their experimental controls indicated that these changes could not be attributed to the ether narcosis employed. The changes they describe are, however, slender, in some ways obscure, and nowhere far from the normal or accidental range. But this method of attack on the aetiology and pathogenesis of schizophrenia is of interest and holds some promise. It is to be thought of in connexion with other lines of attack—e.g., physiological and electro-encephalographic. Schizophrenia is commonly looked on as

[1] Eldridge and Reed, *Arch. Neurol. Psychiat.*, 1938, **40**, 227.
[2] See Scholz, *Z. ges. Neurol. Psychiat.*, 1933, **145**, 471.
[3] *J. Psychol. Neurol.*, 1929, **38**, 155.
[4] *Arch. Neurol. Psychiat.*, 1944, **51**, 155.

progressive disease, or as a "process" taking place in the brain; but the occasional reversibility of signs and symptoms even in chronic and demented cases suggests that gross structural changes are unlikely. It is, perhaps, more probable that the final clue will be found in a deviation of brain metabolism, which once started tends to perpetuate itself in a vicious circle.

VITAMIN C AND CALCIFICATION

It is well established that adequate amounts of vitamin C are necessary for the laying down of the organic matrix of bone, but until recently it was not known that the vitamin is necessary for the production of bone salt. Thus Wolbach and Bessey[1] have stated that vitamin C plays no part in the process of calcification, and Boyle, Bessey, and Howe[2] reported that calcification continues in the teeth of guinea-pigs even when they have been a long time on a scorbutic diet. Bourne[3] of Oxford has recently described experiments the results of which suggest that the deposition of bone salt in normal and regenerating bone is retarded in scorbutic animals, but not in the bone of animals receiving adequate amounts of vitamin C. In the normal animal it would seem that so long as there is sufficient vitamin C to produce the organic matrix of bone the matrix will be calcified. The apparent failure of certain bones to deposit bone salt in scurvy may be due to the fact that there is no matrix on which the calcium may be deposited. It will be recalled that the earlier workers on bone formation and vitamin-C deficiency used lemon and orange juices as sources of vitamin C. Bourne has shown that it is actually vitamin C and not associated substances, such as vitamin P or citric acid, that is responsible for the laying down of the bone matrix and the deposition of calcium salts. Both vitamin P and citrates were devoid of any effect. He suggests that the function of vitamin C in bone formation is to facilitate the production not only of bone matrix but of bone matrix impregnated with phosphatase. The association of vitamin C with phosphatase activity in bone has been confirmed by Schwachman and Gould,[4] who have shown that there is a reduction of both bone and serum phosphatase in scurvy. There is no evidence at the moment that vitamin C is the coenzyme of the phosphatase in calcification. As Bourne points out, the apparent reduction of phosphatase activity in scurvy is probably due to a reduction in the amount of bone matrix produced, rather than to a reduction in phosphatase *per se*. Any matrix formed at all in vitamin-C deficiency will probably be as heavily calcified as the matrix formed in normal animals.

SICKNESS ABSENCE IN INDUSTRY

The importance of recording the sickness absence of their workers is recognized by many if not by most large industrial organizations, for such records enable them to determine their effective labour strength and to gain knowledge of the influence of various conditions of work on the health of those employed. Unfortunately the methods adopted by different firms lack uniformity, so it is often impossible to compare the sickness rates of the firms by valid statistical methods. A uniform method of calculating sickness rates is therefore an outstanding need, and a committee of the Industrial Health Research Board has now issued a preliminary report[5] with the endeavour, in the words of the report, of making "a complicated and, in some respects, a controversial subject as simple as possible." The system of record-keeping recommended has already been put to the test by several large firms, and the cost of the clerical help required appears to work out at less than 4s. per worker per annum. The cards used for the records show the certified and uncertified sickness absence, absence due to accidents, and absences due to other causes, for a two-year period. The disease groups into which the illnesses are classified are seven in number, based on a provisional classification used by the Medical Research Council. Illustrative forms are given by the committee for classifying the causes of sickness, and for the group analysis of absence due to sickness and accidents.

Related, in some of its aspects, to the Health Board's report on sickness absence is the memorandum by the Factory Department of the Ministry of Labour and National Service on medical supervision in factories.[6] This memorandum summarizes the principal duties of a works medical officer, including the examination of the workers under certain conditions, and their interview, or examination, on return to work after injury or illness. It maintains that the works medical officer will have an essential part to play in any schemes for the reconditioning and resettlement of disabled persons in industry, for he has first-hand knowledge of the processes carried out in the factories under his supervision, and of the physical requirements necessary. Thus it is essential for him to make himself acquainted with all the processes in the factory, whereby he may be enabled to assess the relative liability to sickness and injury from each process concerned. Arrangements for first aid and the personnel who carry it out are discussed, the employment of a State-registered nurse (or nurses) being strongly recommended. Medical records of each worker should be kept; these must be under the care of the medical officer, and some attempt at uniformity should be made for purposes of comparison.

A NEW APPROACH TO GOUT

It is well known that chickens, as do other birds, excrete much nitrogen in the form of urates. Apparently if chickens are fed not on the usual grain diet, but on a meat diet, the plasma uric acid rises and deposits of uric acid are formed exactly like the tophi of human gout. Oppenheimer and Kunkel[7] have fed chickens in this way, observing the plasma uric acid to rise from 3 or 4 mg. per 100 c.cm. plasma to 15–17 mg. and tophi to appear in 8 weeks. They have obtained from pig's liver a preparation of uricase which, after purification, they inject into the chickens intramuscularly. This enzyme causes a lowering of plasma uric acid, so that from 50 to 80% of the uric acid disappears in one hour, the effect lasting for varying periods up to 32 hours. Oppenheimer and Kunkel also found that daily injections of uricase kept the plasma uric acid well below that of control chickens over periods of two months. These observations may provide a method of treating gout in human subjects. At present it is not possible because of the large amounts of uricase needed, and it will be necessary to concentrate the uricase considerably before it can be used. The authors have, however, injected into one gouty subject as much as 17 c.cm. of their purest material, and though it did the patient no good they are pleased that it did him no harm. The solution of uricase can be sterilized by filtration.

Lord Dawson of Penn has entered hospital for an operation. He expects to be back at work in seven or eight weeks.

[1] *Physiol. Rev.*, 1942, **22**, 233.
[2] *Arch. Pathol.*, 1940, **30**, 90.
[3] *J. Physiol.*, 1943, **102**, 317.
[4] *J. Nutrit.*, 1942, **23**, 271.
[5] *The Recording of Sickness Absence in Industry.* M.R.C. Industrial Health Research Board Report No. 85, 1944. H.M. Stationery Office. (4d.)
[6] *Memorandum on Medical Supervision in Factories.* Form 327 (Revised), June, 1944. H.M. Stationery Office. (2d.)
[7] *Johns Hopk. Hosp. Bull.*, 1943, **73**, 40.

MINERS' PHTHISIS BUREAU OF S. AFRICA

The report of the Miners' Phthisis Medical Bureau, Union of South Africa, for the three years ended July 31, 1941, records a considerable decrease in the number of initial examinations of miners, partly due to the intensive Army recruiting which followed the German invasion of the Low Countries. In other respects, except for the absence of some members of the staff on military service, the work of the Bureau has not been appreciably affected by the war, for it has been the policy of the Union Government that there should be no curtailment of the activities of the gold-mining industry. With the institution of a more intensive system of seeking out possible cases of pulmonary tuberculosis or of silicosis the number of examinations of native labourers has increased. The Bureau is now housed in a new building specially designed for the purpose. Within it are stored about one million *x*-ray films and the clinical and radiographic records of over 177,000 European and 48,000 native labourers.

From an analysis of a large number of fatal cases of primary cancer of the lung in Europeans it would appear that this disease is no more prevalent among silicotic than among non-silicotic miners or even men working above ground. The Bureau investigated the incidence of silicosis in an iron ore mine at Thabazimbi in the Rustenburg district. In this mine hand-held machine drills are employed, and silica, although present in the ore only in a very small percentage, is reduced by the drilling to extremely fine particles. Examination of a number of European and native workers from this mine showed pathological changes in the lung similar to those produced in a generalized simple silicosis; but in the early stages the lesions were finer than those observed in similar cases among Witwatersrand gold miners. Post-mortem examinations of the lungs of two workers, one European and one native, from the mine shed some light on the pathological condition produced. Earlier radiographs had shown "generalized small mottling" in both cases. The native died later of lobar pneumonia, and the lungs showed widespread haematite pigmentation but no fibrosis. The European died from right-sided cardiac failure. In his case the pigmentation was accompanied by fibrotic changes, and microscopical examination confirmed the presence of a marked degree of sidero-silicosis. Since the enforcement of regulations to reduce the danger from dust in this mine no further serious cases have been seen, and the examination of a cat and several guinea-pigs, which were kept at the working faces for more than a year, revealed only slight deposits of haematite dust and no sign of any fibrosis.

RAPID SURVEYS OF AIR POLLUTION

Atmospheric pollution, which is the chief cause of the difference between the air in towns and the fresh air of the countryside, may in general be said to consist of (1) relatively coarse solid matter, such as ash or grit, which is usually deposited fairly quickly near to its place of origin; (2) fine solid matter, such as smoke, which remains suspended in the air for a relatively long time; and (3) gases, such as sulphur dioxide emitted from domestic or industrial chimneys, engines, etc. It is relatively simple to record the quantities of each of these forms of pollution, and from the records over a period of time to determine whether the pollution in a town is changing in its quality or quantity. It is becoming increasingly important, however, to be able to make more rapid estimates of the distribution of pollution in a particular locality at any given time, because although the normal type of recording apparatus is very simple it cannot usually provide reliable information quickly. Where such information is wanted at short notice—e.g., as part of the consideration of post-war industrial or housing plans—it may be obtained with sufficient accuracy for the immediate purpose by the methods described in a memorandum drawn up by the Atmospheric Pollution Research Committee of the Department of Scientific and Industrial Research, Teddington, Middlesex. The memorandum describes rapid methods of measuring (1) deposited solid matter, (2) suspended solid matter, and (3) SO_2 in the atmosphere. Copies of it, and advice on the conduct of such surveys, may be had from the secretary of the committee.

R. J. Needles and P. D. Gilbert (*Arch. intern. Med.*, 1944, **23**, 113), who record their observations on 125 cases of atypical pneumonia with only one death, maintain that there is an increasing number of cases of an interstitial pneumonitis associated with capillary bronchitis, of undetermined cause or little tendency to excessive mortality. Evidence shows that the cause is to be found in the group of virus-Rickettsia agents. The symptoms and pathological changes strikingly resemble those present in some cases of influenzal pneumonia. Treatment must remain symptomatic until new effective therapeutic agents are discovered.

Correspondence

Pituitary Cachexia

SIR,—The recent paper by Hemphill and Reiss (Aug. 12, p. 211) is of special interest to me, and as the theoretical basis of their treatment is open to misinterpretation I wish to discuss their observations.

Pituitary cachexia (Simmonds's disease) is generally understood to signify the clinical consequence of some organic lesion of the anterior lobe. It is a term which is in less use now than hitherto, as recent observers have stressed that cachexia is not a necessary or even characteristic feature of the disease (Sheehan, 1938). Hypopituitarism (or the more unwieldy term "pan-anterior hypopituitarism") is now more commonly used. Hypopituitarism of a severe degree is invariably due to an organic lesion (primary hypopituitarism), while milder manifestations frequently occur in many wasting cachexias (secondary hypopituitarism). Stephens (1941) has fully discussed the evidence to support this latter contention in the case of anorexia nervosa, but the arguments apply just as well in diseases of malabsorption—e.g., small-bowel diseases—or diseases of metabolism, such as chronic, insufficiently treated diabetes mellitus. Under such conditions, it would seem as if the body conserved itself by stopping growth and menstruation, and lowering O_2 consumption. Spontaneous energy is the last to diminish, and probably depends largely on the efficiency of the adrenal cortex. It is as if the pituitary hormones are progressively inhibited in reverse order of their immediate importance to the survival of the individual.

This general theory of selective pituitary secretion has been advanced in a preliminary communication by the author in 1943. Since then a reasonable amount of clinical data has been accumulated to support it. Some evidence suggests that if the cachexia is secondary to a subacute or chronic infection—e.g., tuberculosis—the pituitary reacts by inhibiting growth and gonadotrophic hormones and increasing the secretion of at least corticotrophic hormone. The idea of the pituitary switching from the less essential to the more essential hormones in times of stress was originally put forward by Selye (1936) from studies in rats. The application of these views to clinical endocrinology would tend to avoid confusion and make more explicable to students some of the commonest types of endocrine disturbances, such as amenorrhoea or retarded growth and sexual development secondary to some not too obvious disease elsewhere. It would also explain some of the vagaries of diabetes mellitus.

Presumably, therefore, Hemphill and Reiss have been dealing with an example of mild hypopituitarism secondary to a distaste for food coupled with mental symptoms. The anorexia caused the cachexia, and hypopituitarism followed—just as it would if the patient had carcinoma of the oesophagus. In fact, their patient started to get well when the appetite returned. It does not follow, as one might be tempted to deduce, that corticotrophic hormone is indicated in any wasting condition of obscure origin even with biochemical evidence of hypopituitarism. I mean in no way to minimize the importance of their observation in the particular type of patient they reported. So far as I am aware the accepted basis of treatment in such emaciated mental cases is intensive and even forced feeding to improve their general health. Hemphill and Reiss may well have found a more superior therapy in corticotrophic hormone, and it is not improbable that adrenal cortical extracts, with salt and D.O.C.A., would have achieved a similar success. Possibly this patient was in a vicious circle in which the loss of appetite caused a hypopituitarism which in turn lowered the general health and further exaggerated her mental condition with its associated anorexia. The fact that their patient continued to improve long after the injections were stopped substantiates the view of a temporary inhibition of the anterior-lobe secretion (secondary hypopituitarism) rather than a true "pituitary cachexia."

I have recently observed the response to corticotrophic hormone in a patient suffering from typical Simmonds's disease (due to postpartum necrosis). After seven days the patient noticed a general sense of well-being with improved appetite and diminished asthenia. By twenty-seven days the weight had increased 5 lb. (to 108 lb.) and the B.P. had increased from 95/60 to 100/70. Notwithstanding injections for over three weeks there was no further improvement. The insulin tolerance was not appreciably improved at any stage of the treatment. The patient deteriorated in later courses of injections.

suggesting the formation of antihormone, although it is possible the extract had lost some of its activity. The response, therefore, was entirely different, as one would expect, from that observed by Hemphill and Reiss.—I am, etc.,

Dublin. D. K. O'DONOVAN.

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Intramuscular Quinine

SIR,—Sir Philip Manson-Bahr, in the course of his interesting letter on war malaria in the *Journal* for Sept. 9, refers to the efficiency of intramuscular injections of quinine. From an experience of 20 years in East Africa, during which I have given some thousands of injections, I can heartily endorse Sir Philip's observations. Intramuscular injections are particularly useful in cases of pregnancy, and where incessant vomiting is a bar to oral administration. There are two points to which I wish to attract attention. First, the site of the injection should be thoroughly and deeply massaged for a full minute to disperse the acid and to dilute it with the body fluids. I have never had a case of sloughing or paralysis, but have seen several where this ritual has not been performed. The second point is that a mineral acid would not seem to be the best vehicle for an intramuscular injection. I would suggest lactate of quinine, in which the acid is a normal product of muscle metabolism, should be more suitable theoretically. Unfortunately I can find no reference to its solubility, though other hydroxy acids, such as tartaric, produce a soluble salt. The point is worthy of further investigation, I think.—I am, etc.,

Slough. W. L. PEACOCK, S.M.O., Uganda (ret.).

The Metric System in Medicine

SIR,—Prof. W. C. W. Nixon's plea[1] for the exclusive use of the metric system in medicine comes at a singularly opportune moment: (i) there is every indication that there will be extensive changes in medical organization and practice in other directions; (ii) limitation of supplies of drugs has altered prescribing habits, and tended to favour drugs—e.g., sulphonamides—which are dispensed metrically; (iii) the many men who will be returning from the Services to civilian practice should find it relatively easy, among the much greater adjustments that they will have to make, to assimilate this reform. It seems improbable that such a favourable combination of circumstances will recur.

While there may be strong arguments against the change to the metric system in engineering, the case for retaining imperial and apothecaries' units in medicine is surely very feeble. It has been argued that the older systems provide more convenient doses, but even this dubious advantage is fast disappearing with the increasing number of metrically dosed synthetic drugs. Further, the arbitrary "t.d.s., p.c." convention of dosage tends to be replaced by a rational schedule designed to bring about the necessary concentration of the drug in the body fluids for the necessary time. It is inconceivable that concentrations of drugs in the body would ever be measured in terms of grains per pint, and with changing conceptions of pharmacotherapy the position has almost been reached at which the system of mensuration used for a drug, with the exception of a few active principles of plants and inorganic compounds, may be regarded as an indicator of its value.

There is no point in pleading for the use of the metric system by medical scientists, because they have adopted it without question. It is only in medical and pharmaceutical practice that the older units survive as worthless anachronisms. Quite apart from the relative merits of the different measures, the existence of a dual system of mensuration in medicine is an intolerable anomaly. It is not uncommon for prescriptions to contain a blend of imperial and metric units, or, as Stehle[2] has pointed out, for ampoules to be dispensed according to metric volume and imperial weight—e.g., "ephedrinae sulphas, 3/4 gr. in 1 c.c." Stehle has also drawn attention to another absurdity: "Year after year, when medical students reach the clinical subjects, they abandon the most satisfactory system of weights and measures ever devised and adopt either the imperial or apothecaries' system. . . . They do even more than this. They adopt Roman numerals in preference to Arabic and signs in preference to words." What is the value of these signs? They are of such antiquity that the date of their introduction and their original significance are matters for dispute,[3] and they have the serious practical disadvantage that their use is a notorious source of prescribing errors. They, and the use of grains, minims, and drachms, belong to a vanished age which was entertainingly described by Sir Clifford Allbutt[4]: "When I began practice it was customary at every consultation to prepare a writing-table, pens, and ink for 'the prescription.' This script, even in my young days, was of formidable composition, a drug for every symptom, and a few more for the pool; it was solemnly set forth, and signed by two or more physicians; by the patient's friends this was understood, if but long enough, to be the organ of his restoration. No occasion was left for modification according to circumstances, or the various phases of the disorder; to it the doctor in attendance was to be as submissive as the patient to whom it was scrupulously administered. . . ."

Although prescription writing is no longer an "art," and consultations are less of a pantomime, the old measures and signs remain as relics of obscurantism, and of ignorance masked by pomposity and pretence. If any should regard the proposal to abandon imperial and apothecaries' measures in medicine as premature, they will be relieved to know that, 118 years ago, Andrew Duncan senior pointed out,[5] at the respectable age of 82, that their use was "attended with many inconveniences," and suggested that "without adopting the new French weights" we should imitate them by using decimal multiples of the grain. Duncan did not give any reasons against the metric system. Possibly, as a recent product of the French Revolution, it was not considered acceptable. The *Lancet*[6] approved Duncan's suggestion in principle, but recommended that "instead of adopting an alteration of weights for pharmacy, as proposed in this letter, it would be more advisable to wait a little, until the Government shall ordain the decimal proportions of weights and measures to be generally used, which we anticipate to see done in a few years." Although other countries, one after another, have adopted the metric system, and its claims in medicine have often been reiterated, the *Lancet's* prophecy remains unfulfilled after nearly a century and a quarter.

Some further reasons against adherence to imperial and apothecaries' weights and measures may be summarized as follows: (i) Their use is a formidable barrier to the understanding of British medical literature by medical men of most other countries. (ii) They are a source of ambiguities—for example, "ounce" is often used in such a context as to make it difficult to determine whether solid or fluid measure is intended. (iii) A dual mensuration in medicine is not only irrational but dangerous—"gr." means "gramme" in Continental and "grain" in British medical literature, and the confusion of these two units has, even in this country, caused many accidents. (iv) The relation between imperial and apothecaries' units is confusing. (v) The range of units available is inadequate for present needs. (vi) Calculations are laborious. (vii) There is no simple relation between linear, solid, and fluid units.

In December, 1943, the Council on Pharmacy and Chemistry of the American Medical Association gave[7] its reasons for the exclusive adoption of metric quantities and dosages in all its publications, and concluded: "The universal adoption of the metric system would be a manifestation of rationality and of interprofessional and international co-operation of high practical utility." In this country the Pharmaceutical Society has recently said[8] that "there is no doubt that the pharmacist finds the metric system more easy, convenient, and, what is as important, nearly fool-proof."

There may be some who think that it would be difficult to abandon the old habits of mensuration. The experience of working before the war for 18 months in a country in which the metric system was exclusively employed convinced me that the change could be made very easily, and that the advantages of working metrically not only in medicine but in the kitchen, the nursery, and the improvised dark-room of the amateur photographer, were considerable.

In the light of these considerations, there would seem to be no valid reason for continuing to make ourselves unintelligible to our medical colleagues in other parts of the world. I

[1] Nixon, W. C. W., *British Medical Journal*, 1944, **2**, 320.
[2] Stehle, R. L., *Canad. med. Ass. J.*, 1942, **46**, 463.
[3] Wootton, A. C., *Chronicles of Pharmacy*, Vol. 2, London, 1910.
[4] Allbutt, C., *Greek Medicine in Rome*, London, 1921.
[5] Duncan, A., *Lancet*, 1826, **11**, 144.
[6] *Lancet*, 1826, **11**, 143.
[7] Council on Pharmacy and Chemistry, *J. Amer. med. Ass.*, 1943, **123**, 900.
[8] *Pharmaceutical Journal*, 1944, **152**, 221.

suggest that it would be fitting for the *Journal* to take a lead in this matter by asking all contributors to use metric units or to give metric equivalents to other units in parentheses.—I am, etc.,

N. HOWARD JONES.

SIR,—Many readers will agree with Prof. W. C. W. Nixon (Sept. 2, p. 320) that the time is opportune for the adoption of the metric system in medicine. This development—which is ultimately inevitable—is being allowed to take place gradually, but haphazardly, and is a potential source of much confusion and error which could be avoided or passed over quickly by a deliberate change from one system to the other. I agree with your correspondent that the best opportunity likely to occur for many years will present itself in the near future.

If the present rate of medical progress is maintained, doctors will soon find themselves in a position to appreciate that a clear decision is necessary. In medical research, and in laboratories providing routine services for the medical profession, the metric system is established. Whenever scientific methods are applied in medicine the metric system is employed as a matter of course. This will affect the general practitioner; as research becomes more closely integrated with clinical practice, and the use of laboratory facilities is extended, he will find himself forced to adopt the metric system also, or be prepared to perform a series of mental acrobatics at increasingly frequent intervals. Already the metric system is used where applicable for reporting the results of laboratory tests, and I have heard no complaint on that score. Blood sugar, for example, is given as so many milligrammes per 100 c.cm. Toxicity is stated in terms of grammes per kilogramme body weight, and, logically, dosage is sometimes computed on a similar basis; a little thought will bring to mind several similar instances. Doctors are familiar with the use of the metric system in parenteral therapy, although they persist in using solutions containing so many grains per c.cm. The vitamins, minerals, and the newer therapeutic preparations, such as the sulphonamides, the synthetic oestrogens, local anaesthetics, pethidine, hexobarbitone, mepacrine, and others, are being prescribed in metric doses without—so far as I am aware—any great strain in the consulting room. This tendency is obviously going to become more extensive, with at least one unfortunate consequence. I have already seen prescriptions in which the dose of one ingredient was stated metrically while the others were according to the apothecary system. This is not only ridiculous, it is potentially dangerous. It is not always easy to determine whether grains or grammes are intended, and if these expressions in their abbreviated illegible forms are to appear in one prescription trouble must be expected. A deliberate adoption of the metric system might not eliminate all possibility of confusion and error, but it would limit their duration to as short a time as possible, and, I forecast, would not cause very much more disturbance than the introduction of a new edition of the *B.P.* or the *National Formulary*. Doctors may take a second or two longer to write a prescription, but if the result is greater clarity who can object?—I am, etc.,

Greenford, Middlesex. J. THOS. MARSH.

Pentothal Anaesthesia

SIR,—We have been looking forward each week recently to the *British Medical Journal* with much more interest than usual, in order to read the latest notions about anaesthetics, especially pentothal. In this department pentothal has been almost exclusively used since its introduction, as being most convenient and the safest anaesthetic for radium insertions and minor operations; and, since no fewer than 100 cases per annum are done, one of us at least (R. R. M.) can lay claim to considerable experience of it.

The cases represented by those requiring radium insertions form, in our opinion, the worst group of anaesthetic risks in the surgical field. Few patients are under 50 years of age, most are over 60, and many are between 70 and 80. The vast majority have arteriosclerosis to a more or less marked degree, and many have demonstrably poor myocardial function. Not a few are obviously toxic from their neoplastic process. Yet we have not one case to record of an anaesthetic death, either on the table or in bed after operation. Only on rare occasions, when an inexperienced anaesthetist has allowed partial asphyxia to occur, has operation had to be suspended. We have never seen vomiting on the table; it has happened—mildly only—in a very few cases during the stage of recovery. Laryngeal spasm has been met with once or twice, but only when the patient has been allowed to become too lightly anaesthetized; when it does occur it proves most intractable, even if the anaesthetic is then pushed. Bronchopneumonia, which is very frequent in radium needling of the mouth region under inhalational anaesthesia, has been practically abolished by the routine use of pentothal.

Briefly, our routine technique is as follows:

1. Premedication: morph. sulph. gr. 1/4 and atropine sulph. gr. 1/100. This appears to lessen the requirements of pentothal.

2. 1 g. of pentothal in 20 c.cm. is used. More than this has never been necessary for our purposes, the average length of anaesthesia in our cases being 15 to 20 minutes. Long intravenous needles with a short bevel are used. The largest antecubital vein (variable in position) is chosen. The skin is wiped with spirit, an elastic bandage tourniquet applied, and the patient told to open and close the hand while the surgeon is scrubbing; ample time is thus given for the veins to become prominent.

3. When the vein is entered, the tourniquet is removed and the patient asked to count out loud. Induction is rapid—at the rate of approximately 1 c.cm. every two seconds. The counting almost invariably stops at about "16." Another 3 c.cm. is then given and administration is stopped. The average amount required for induction is 8 to 9 c.cm.

4. Further pentothal is given, 1 c.cm. at a time, as indicated. We find that when the patient is fully induced, as described above, the breathing is inaudible and one has to watch closely to perceive respiratory movement. The criterion adopted is that when breathing becomes audible more is required. We find that if this rule is not followed, face-twitching or slight leg movements soon begin. During the whole anaesthesia positive pressure is kept on the syringe plunger to prevent blood reflux and clotting within the needles. So far this accident has not occurred.

The main difficulty experienced in all pentothal cases is the inveterate tendency of the tongue to become completely flaccid and fall back. Probably the tendency is not greater than in ordinary anaesthesia, but it assumes greater prominence as the anaesthetist is away from the head and unable to exert manual control of the jaw. We have now adopted the practice of employing tongue forceps almost as a routine, handing them over to an assistant. A small point of technique, which we find makes a vital difference in a busy theatre where two or three pentothal cases are following in quick succession, is as follows. The needles, freshly sharpened before each theatre day, arrive in the theatre in brass trays: they remain in these during sterilization, and are removed only immediately before use. Blunting by hitting against dishes, etc., is thus avoided. This rule about needles is strictly enforced. Pentothal has accidentally been spilled into the tissues on a few occasions, but not once recently has there been any local reaction. For some time we ordered hot fomentations on return to bed in such cases, but have given these up without ill effects. Some months ago reactions sometimes occurred after spilling, and in two or three cases caused sloughing, which healed without difficulty. It is thought that some abnormality in materials may have accounted for this.

In conclusion, our judgment is that pentothal is not only ideal for the special purpose of a radium therapy department but has also proved very safe in a series of unselected cases, including many bad risks. It appears to us that any patient who is clinically likely to survive more than a month is a safe risk for pentothal. We now give it without hesitation to patients in the seventh and eighth decades; to those with cardiac irregularities, often gross; and to those showing obvious signs of toxaemia. Many of the anaesthetics in our series have been given by inexperienced house-surgeons under guidance from the surgeon. On other occasions more senior residents have acted as anaesthetists. Probably not more than 10 inductions have been given by specialist anaesthetists. The last 50 or so cases have been anaesthetized by one of us (D. M. M.) without the surgeon on any occasion requiring to cease operation or to give any attention to the patient so far as the anaesthesia was concerned.—We are, etc.,

ROBERT R. MORRISON, M.B., D.M.R.E.
Medical Officer in Charge, Radiotherapy Department, Glasgow Royal Infirmary.

DONALD M. MACKAY, M.B.,
Ex-Resident House-surgeon, Glasgow Royal Infirmary.

Pentothal in Nasopharyngeal Operations

SIR,—There has been so much oral discussion and printed correspondence about Dr. E. R. Dingle's and Dr. F. W. Roberts's letters that appeared in your *Journal* of July 29 and my letter of July 15 that I should like to state that I agree with Dr. Roberts's first point.

If I were an anaesthetist I should refuse to give sodium pentothal unless the operator packed off the nasopharynx with gauze and had an aspirating motor beside him. The anaesthetists who anaesthetize my patients insert a metal airway into the mouth during the induction of anaesthesia, and then, when the patient is asleep, they insert a rubber airway which passes over the back of the tongue, and through this a catheter is passed for the administration of oxygen. Before I begin operating on the nose I pass a piece of gauze with tape attached into each nostril, passing the gauze into the nasopharynx and letting the tape lie on the floor of the nose to facilitate its removal. Besides this I have a hand electric suction motor to suck blood from the pharynx in case the pharyngeal dam is ineffective.

In a tonsil dissection, after the patient is under the sodium pentothal I introduce a Boyle-Davis gag, extending the patient's head by placing two pillows under his shoulders. This position allows the blood to flow into the nasopharynx, from which it can be aspirated by the suction motor. If general anaesthesia is necessary following on the sodium pentothal a Magill tube is introduced, and, in future, when a Magill tube is used I would recommend that Rowbotham's balloon be used (*Lancet*, July 1, 1944), which will certainly prevent any aspiration of blood into the bronchi.

As regards Dr. Roberts's criticism on the use of picrotoxin, in future I shall accept his criticism and use leptazol, which is as active as picrotoxin if given in larger doses than picrotoxin, and is certainly more potent than coramine.

As regards the dose of morphine, it is true that I have used 1/4-gr. doses, but on account of recent criticism I have cut it down to 1/6—giving morphine 1/6, scopolamine 1/200, and atropine 1/100.

As regards Dr. Dingle's letter, he states he gained the impression that the death of my patient was considered to be due to primary cardiac failure. That does not mean that Dr. Dingle himself believed that death was due to that cause—merely a piece of politeness showered on me—for he has told me in conversation that he knows that sodium pentothal never produces primary cardiac failure, but that it always first produces respiratory failure, and it is for this reason that he has planned his treatment.

I hope now that young anaesthetists will be armed with rules, and will have the courage to enforce them—i.e., not operating without oxygen and an aspirator, having proper packing off of the nasopharynx, and in case of necessity using leptazol.—I am, etc.,

Harrogate. W. S. THACKER NEVILLE.

Sulphonamide Sensitivity

SIR,—I would like to support the warning given in your leading article (Aug. 19, p. 248) about the dangers of sulphonamide sensitivity. I have recently seen several cases in which rashes have been produced by sulphaguanidine so that the patient who was originally suffering from a mild diarrhoea has been off work for weeks because of his skin. In some of these cases the patients already knew that they were sensitive to sulpha drugs but did not realize what was being given to them, which shows the importance of taking an accurate history before starting treatment. Sulphaguanidine is a great saver of manpower, but neither it nor any other sulpha drug should be given until it is certain that the patient has had no previous skin reaction. There are, of course, exceptional cases where the risk must be run.

One point in diagnosis is worth recording. Rashes from sulpha drugs are often difficult to diagnose from German measles, especially as glandular enlargement is said to occur in both. However, a careful search will often show small papulovesicular lesions on the backs of the hands and fingers in the former which will settle the diagnosis.—I am, etc.,

F. F. HELLIER,
Lieut.-Col., R.A.M.C.

Rate of Artificial Respiration

SIR,—Now that uniformity as regards the timing of Schäfer's method appears to have been attained, may I enter the lists and point out that no uniformity exists as regards *rate* either in this or in Eve's rocking method. Whereas the St. John's textbook and those of the Royal Navy, Army, and Royal Life-Saving Society advocate 12 times a minute—approximating normal respiration—the B.R.C.S. *First Aid Manual* advises 15 to 18 times a minute—a possible 50 % increase. Again, Dr. Eve, in a communication in the *Lancet* (about April, 1944), recommended 10 double rocks a minute—4 seconds head down, 2 seconds feet down. But Surg. Lieut. Gibbens (*Journal*, Dec. 26, 1942) advocated 12 to 15 double rocks a minute—again a possible increase of 50%—whereas your leading article (June 24, 1944) suggests 8 to 9 rocks a minute—4 seconds head down, 3 seconds feet down.

Truly the way of the instructor is hard, and he may well join with Macbeth and say,

> ". . . we do but teach
> Bloody instructions, which being taught, return
> To plague the inventor."

—I am, etc.,

Guildford. J. L. BARFORD.

Postgraduate Medicine

SIR,—Dr. Walshe's considerations on higher or postgraduate medical studies are bound to make a great impression on the readers of the *Journal*. They are so carefully collected and so ably presented that one's first reaction is to applaud the resonant note. It is only on deeper percussion that the tympanitic sound becomes apparent. The reason is the common one: the premisses are fallacious.

First, he presumes that medicine is a science. Although it should have a scientific basis, it is still, thank God, an art—an art which cannot be mastered in the monastic precincts of "the good postgraduate school" set aside "for advanced and original studies." Secondly, there is the presumption (in both senses of the word) that the general practitioner is of lesser breed, unworthy to be associated with the blue-blooded aristocracy of the "consultants and specialists." Where, oh where, would medicine be now but for the host of general practitioners who have been responsible *while in general practice* for the advancement of our knowledge? One has only to mention such names as Edward Jenner and James Mackenzie utterly to refute such an aspersion. Lastly, there is, without a shred of evidence, the wholesale damnation of "refresher courses." Admittedly these courses vary in their value. Some are bad, some indifferent; the majority are extremely good. Let Dr. Walshe do a little research work on his own, and take, say, fifty doctors who have never attended a refresher course and fifty who make a habit of it, and then judge, on his own standards, which are the better doctors.—I am, etc.,

Torquay. B. VENN DUNN, M.D., F.R.C.S.

SIR,—In your issue of Sept. 2 Dr. Walshe makes some interesting and important points about the future of postgraduate medicine. Writing as a teacher, he rightly stresses the value of the special hospitals and the need to encourage research, instead of creating cram courses and diploma machines. From the student's aspect, however, there are also one or two things to say. While it is essential to have schools devoted, like that at Hammersmith, to the advancement of higher medicine, it is also necessary to have some institution which caters primarily for the need of the general practitioner. Short "refresher" courses, given by a number of consultants and specialists without a knowledge of the problems arising in general practice, do not benefit those who attend them. The student picks up a scattered handful of unrelated facts, many of which are not applicable to his daily round. A syllabus created by those with intimate knowledge of the requirements of the general practitioner, from personal experience, might be more useful to the postgraduate. Also, it is certain that the short intensive course is less stimulating and informative than, say, an afternoon a week for three or four months spent in the out-patient department and wards of a hospital as clinical

assistant to an honorary physician or surgeon. The intervals between visits give time for meditation on what has been seen.

As practical therapeutics is an important part of general practice, facilities for doctors to learn such things as the injection treatment of piles, simple physiotherapy, and so on, would be very welcome. At present, students waste a considerable amount of time finding the clinics or departments most suited to their needs.

Let us hope, therefore, that in the brave new world of post-graduate medicine there will be some place which caters for the conscious inadequacy of the many, as well as facilities for the more ambitious few.—I am, etc.,

Leighton Buzzard. TREVOR H. HOWELL.

Disadvantages of Lay Psychotherapy

SIR,—In the *Journal* of Sept. 2 a letter was printed supporting the use of lay psychotherapists, and claiming that medical knowledge was not necessary provided the therapist knew sufficient about psychotherapy.

Now "anxiety state" is a condition commonly treated by psychotherapy. Briefly the symptoms of an anxiety state may be listed as follows: *Bodily Symptoms.*—Tachycardia, tremor, sweating, brisk tendon reflexes, raised blood pressure (temporary), diarrhoea, dyspepsia, enuresis, impotence, and so on. *Mental Symptoms.*—Insomnia, headaches, vertigo, all sorts of fears, inferiority feelings, hypochondriacal complaints, etc. Often the patient presents only one main symptom, so that it is necessary to have a knowledge of the differential diagnoses of, say, tachycardia, tremor, dyspepsia, and enuresis, and in my opinion this entails a great deal of both medical knowledge and experience. Again, even when an anxiety state is frankly present, it has to be diagnosed from *organic* disease, as early general paralysis, cerebro-arteriosclerosis, thyrotoxicosis, chronic toxaemias, cerebral injury, etc. Further, an anxiety state may be but a feature of schizophrenia, involutional melancholia, neurasthenia, cyclothymia; or it may be intermingled with hysteria and obsessional disorders.

It therefore appears to me that anyone who undertakes to treat a mental illness should have a sound knowledge not only of psychotherapy but also of psychological and general medicine. There may be a few lay psychotherapists who have had good results, but I think the idea that lay psychotherapists are qualified to treat mental illness is a wrong one, and it is to prevent this idea gaining ground that I have been prompted to write this letter.—I am, etc.,

Edinburgh. KENNETH HAZELL, M.R.C.P., D.P.M.

SIR,—The suggestion of Dr. D. Stanley-Jones that psychotherapists should be trained without their first having acquired a general medical training is surely both hazardous and unmindful of the essentials of successful psychotherapy. I would have thought that it was by now generally accepted that physical and mental illness often go together, and that it was realized that psychotherapy cannot be safely practised without first a correct diagnosis. In which case it surely follows that a psychiatrist requires to be an experienced clinician and neurologist in order to differentiate organic disease from mental illness before he is able with safety to diagnose the different forms of mental illness.

I suppose it would be possible for the psychiatrist to advise the "lay" psychotherapist on the form of treatment, but even so the latter would surely be working at a disadvantage, since he would not be in a position to beget the same confidence that a medical practitioner might be able to gain.—I am, etc.,

M. F. BETHELL, M.R.C.S., L.R.C.P.

Morale in the Services

SIR,—Temp. Surg. Capt. Curran and Temp. Surg. Lieut. Garmany, writing on "Post-operational Strain in the Navy" (*B.M.J.*, July 29, p. 144), were unfortunate in their use of terms when comparing factors contributing to good morale in the Navy with that of the Air Force and Tank Corps. To describe either a tank or an aircraft as a "contraption" shows that in their own admirable devotion to the Senior Service they have lost an appreciation of that wider view which all good psychiatrists should possess. It should be a matter of common knowledge that tank crews feel in a "vividly personal way" about their machines. The five members of a Churchill, for instance, have usually spent two or three years as a small team in constant charge of their vehicle, which they come to regard as an extension of themselves. It is the practice in the Tank Corps to change personnel who "do not fit," thus increasing the idea and feeling of a happy team.

From the numerical point of view it is fairer to compare a ship with a regiment, but although at first sight it might appear that men are more devoted to a ship, I doubt whether in practice this is the case. Even with such a large unit as a Division great personal pride is felt. There is considerable satisfaction experienced in being a "Desert Rat," probably more than in a comparable naval formation. As one officer aptly put it, "It would be a hell of a blow to take down the Divisional sign!"

I have no figures to support this criticism, but I doubt whether the writers had any evidence to support their own attitude towards this particular problem.—I am, etc.,

A. S. THORLEY,
Major, R.A.M.C., Psychiatric Specialist.

Military Psychiatry

SIR,—Lieut.-Col. Craigie's article on military psychiatry and his frank reply to Dr. Shaw's criticism have illustrated the great defect in Service psychiatry. It is clear that in the Services non-medical considerations are allowed to override sound principles of psychiatry to the inevitable detriment of the patient. While it is true that Service considerations will sometimes interfere with correct treatment in other branches of medicine, the conflict does not occur as frequently in somatic medicine as it does in psychiatry.

Since it appears that the war—in Europe at least—will shortly be over, it would be academic to pursue this issue if it were not that Service psychiatric practice will certainly have a considerable influence on post-war medicine. During wartime the psychological element in illness has received much more attention than formerly, and there will be a continuing demand for the help of psychiatrists in dealing with a great variety of minor illnesses, especially those psychosomatic and neurotic diseases which cause so much wastage of man-power in industry. The demand for psychiatrists will presumably be met very largely from those who have been trained under Service conditions. It will be a social disaster if they take with them into civilian practice the Service attitude towards their patients.

It may seem that I am unduly alarmist in suggesting such a possibility. A quotation from Curran and Guttmann's recent textbook on psychological medicine provides evidence in support of my fears. They suggest that:

"Social changes . . . may well lead the community to demand more of the individual . . . and to permit him less freedom of choice and action. It is also probable that what are in fact neurotic reactions to economic stress or to the continuance of regimentation in civilian life will be rationalized as being due to war service and will result in claims for pension and compensation. The wartime orientation of the medical profession as regards the emphasis on its duty to the community rather than to the individual will need to continue in order to deal satisfactorily with problems of this kind" (p. 141, op. cit.).

It requires little imagination to foresee that a social system demanding the "continuance of regimentation in civilian life," in which the industrial misfits are dealt with by a corps of psychiatrists whose first duty is to the "community," would be uncomfortably like the totalitarian regimes of the Continent. If, in addition, the psychiatrist's duty to the community is reinforced by his enrolment in the State Medical Service, so that he lacks even the monetary inducement to put his patient first, then individual liberty will be still further menaced. Since it seems inevitable that society will be much more planned in the future, I hope that the medical profession will be concerned to mitigate the pressure of such planning when it bears too hardly on the individual, and that once the stress of war is over the first duty of a doctor will again be to his patient.—I am, etc.,

Carlisle. J. BERNANT PHILLIPS.

Service Medicine

SIR,—The letter from Dr. P. B. Corbett (*Journal*, Sept. 9) is revealing, if revelation was necessary. Of course the advantages of the R.A.F. Medical Services, and those of the R.N. and the Army, are great from both the patients' and doctors' points of view. No one doubts it. But there are "buts." (*a*) The complete history sheet is of the greatest value while the man is in the Service. If and when he is discharged it becomes so much waste paper. The man is not told the grounds on which he is discharged, nor the findings of a medical board. His medical attendant is equally left in the dark. (*b*) Expensive drugs and appliances are supplied generously and promptly. (*c*) The observation wards are the greatest boon. (*d*) Specialists of high standing are always on tap. (*e*) Adequate trained clinical and clerical assistance is always to hand. Obviously all these are admirable from both the patients' and the doctors' points of view. They are what the medical profession are pressing for through the B.M.A., and they are what the Government are extremely unlikely, and probably unwilling, to provide on account of the cost.

In wartime the civilian has little value in comparison to the man in the Services; and so far the same appears to be the official attitude in peacetime. One further point is that Dr. Corbett appears to be fortunate in his superior officers (which is not always so); but would it be equally pleasant, or work so well, if those superiors happened to be a Ministry official, an appointed administrative officer, or some "local authority"? The majority of doctors with experience of such conditions think it would not.—I am, etc.,

Deddington, Oxon. G. M. HODGES.

SIR,—On reading the letter by "Temporary Serving Officer" (Aug. 19, p. 255) one can only assume that he has something wrong with his make-up or that he has had a bad time at the hands of Service medical administration or that he has not obtained the promotion and recognition to which he considers his professional ability entitles him. It is also obvious that he has little or no knowledge of either Service or civil medical administration, or he would hardly be willing to hand it over to laymen. It is against rash and ill-informed statements such as he has made that we have to be very guarded, especially at a time when we are fighting for the control of our own professional destiny.

The sudden and rapid expansion of the Services, and the difficulties under which the civilian medical services have accordingly had to work, have called for and obtained the highest administrative capabilities. It is, indeed, a matter for congratulation rather than the abuse which your correspondent has seen fit to heap upon it. Does he seriously suggest that the organization of the Army Blood Supply Centre or the evacuation of thousands of casualties from Normandy—to name two problems only—could have been dealt with by laymen? Surely the officers who devised the policy in these two cases and their assistants who administered it are worthy of the rank and pay which go with it.

It is also necessary to point out that the medical administrator's duty towards the sick does not—like that of the hospital clinical staff—end with the patient's discharge from hospital. He has to peruse carefully those despised "redundant documents"—simple documents which it appears that many temporary serving officers are quite incapable of completing properly—in order that the sick man's interest may be fully safeguarded in years to come.

Another point upon which your anonymous correspondent is quite ignorant is that most Service medical administrators are the representatives of the profession on formation headquarter staffs. In this capacity they not only have to administer policy laid down by higher authority but also make decisions on domestic matters in their own formations. It is therefore obvious that they have to be not only doctors but men of considerable experience in Service matters. It is also obvious that they must be given sufficient rank in order that medical policy may be fully stressed and enforced. It is in this way that the despised ex-regular officer has been of the utmost value to the State. That there are misfits in all branches of the Service cannot be denied—there always will be. "Temporary Serving Officer" would appear to be one of them. My own experience of Service administrative medical officers is that they have been kindly, helpful, and co-operative, but men who do not suffer fools gladly.

There is no doubt that some form of State Medical Service is coming, and the profession is agreed that its administration must be in the hands of doctors. The administration should be neither master nor servant of the profession, but an integral part of it; one part cannot work without the other. Therefore let the medical policy of the State be devised by representatives of all parties concerned, duly appointed in accordance with democratic principles, let its administrators be well-qualified doctors who have a flair for this kind of work, and let all branches of the profession work together as a team for its professed ideals.—I am, etc.,

C. H. PAULI,
Major, R.A.M.C.

Medical Services—Home and Colonial

SIR,—Readers of the *B.M.J.* who have had any lingering doubts of the democratic outlook of its editorial panel (and these doubters have not been few) must surely have had those doubts dispelled during the past year by the publication *inter alia* of Dr. Geoffrey Bourne's several articles on State medicine, and more recently by the letters of Dr. H. B. Morgan on July 1 on the Colonial Medical Service, and by "Temporary Serving Officer" on Aug. 19 on Service medicine. The ethical and political importance of this stand should be appreciated by all doctors, especially those in the Services at home and in the Colonies, as these have no other organ through which to voice their opinions and to afford them moral support. I have had many opportunities to hear from my colleague in the R.A.F. evidence which confirms the views of "Temporary Serving Officer." But it is of the Colonial Service I would write, having served in the Gold Coast from 1925 to 1942. "Temporary Serving Officer" has been obliged to preserve his anonymity, but I am not so handicapped, having resigned from the Colonial Medical Service in 1942.

I would first recall Dr. Morgan's letter. Colonial medical officers who read that letter were not at all likely to have misunderstood its implications, nor were they likely to be distressed by his alluding to the Colonial Service as the "worst medical service in the world." They might, however, have been more pleased had the denouncement been accompanied by precise evidence. Therefore I would myself recall certain faults, and offer some constructive criticisms of the Service as I knew it in West Africa.

At the outset a critic of the Colonial Medical Service should bear in mind its history and constitution and its character—which is somewhat military. Uncritical and unquestioning obedience is expected; enterprise or initiative is not required. Until recent years medical officers entered the Service to treat only the officials and their families. Against this imperial background an officer of conservative mind might express gratification with the rate of progress and with the transition to a medical service for the whole community. But to a modern and democratic medical mind much fault is still to be found. The observations made hereunder represent the opinions expressed by many medical officers in the course of years.

(i) The medical service is subordinate to, rather than complementary to, the political administration (which is itself subordinate to trading interests—as all may perceive). It has not, and never has had, a comprehensive health plan or policy for the colony as a whole, and there has been neither purpose nor goal to inspire M.O.s; merely dull routine (although an officer may engage in research *on his own initiative*). (ii) It is mainly because of this that the sole official record of work done is the scrappy annual report furnished by the director, together with that unscientific compilation of figures, Medical Form I. (iii) The personal relationship between the director and the medical officers has usually been a poor one. His office, that of an administrator, removes him from professional contact and from interest and sympathy in the work of the medical officers. A keen professional interest, I believe, there never has been. The following personal experiences may illustrate these points:

(i) In 1933 I worked keenly and became fairly expert in the problems of sleeping sickness and tsetse-fly distribution in South Mamprussi in the Northern Territories. By the end of the year I had drawn up and submitted a programme of bush clearing to cover a wide area. Thereupon I was removed and replaced by an

M.O. who had never been in an out-station before; a *tired* officer who had asked for a rest from a busy hospital! (I would not suggest that such ineptitude is usual, but it happened.)

(ii) In 1936, from Oda in the Ashanti forest, I submitted a lengthy report to the director on the incidence and course of a fatal childhood pellagra syndrome prevalent in that region. About a month later I succeeded in having the report returned to me. It was unacknowledged. Some two years later I learned that in that year—1936—not thirty miles away from me, Clarke, a keen biochemist, was investigating (at his own expense) the experimental pathology of a similar condition in rats. Had we known of each other's work useful collaboration might have been arranged. This experience gave me much food for thought on the need for official interest in medical research on the Gold Coast.

(iii) In 1939 I was seconded to conduct a diet and nutrition survey of natives in selected areas of the Gold Coast. In April, 1941, I submitted a 200-page report covering two years' investigations. This report, although approved by the Nutrition Committee in Accra, was not sent home. Inquiry at the Colonial Office during leave left me in no doubt that this action was in accordance with their wishes. Therefore I resigned from the Service.

I would now, with the detachment which maturity brings, on behalf of my silent serving colleagues, make certain constructive criticisms.

1. The role of Director of Medical Services should be to direct clinical medicine and research. Therefore the officer appointed to that post should have a positive record of achievement in the clinical field. The financial and administrative duties to which he normally gives so much time should be undertaken by administrative officers. (In a general way it is true that science is rated secondary to its financial costs, which receive an inordinate amount of official attention.)

2. The Director must needs be appointed by Government; yet the appointment might be made subject to a majority approval vote by all medical officers confirmed in rank. I am conscious of the revolutionary nature of this proposal; yet any courageous doctor may earnestly inquire, "If the Service is to develop on truly democratic lines why should *not* the responsible doctors be consulted?" (The need for such a change step is to be found in the appointments that have been made hitherto.)

3. The greatest professional disadvantage of medical officers in West Africa is the lack of opportunity for exchange of views and ideas. In 1936 many senior M.O.s wrote a proposal to the then D.M.S. requesting that clinical meetings be held once or twice yearly at regional centres—Accra, Sekondi, Kumasi, Tamale. The political officers hold yearly conferences. The request was ignored.

4. A medical service with some 50 medical officers serving some three million people should have at least one highly qualified medical registrar at headquarters, assisted by a special clerical staff, whose duties would be to aid the director in guiding research, to collate clinical records, to criticize, and to advise M.O.s. This expert staff could edit a local medical journal. (The *West African Medical Journal* died in 1927 because there was no staff available to run it.)

5. A medical library of books and periodicals should be provided. This could be suitably controlled by the officers above mentioned with additional clerical library staff. (Hitherto medical officers have been able to obtain the loan of some books from Accra by courtesy of the pathologist.) It would seem in the official view that medical journals and a library can be conducted by officers in their spare time; or, it might be truer to state that such institutions do not interest Government at all.

6. Publication of, and verbal expression of, professional views and opinions should be *free*. (It should be of the keenest interest to doctors at home that similar repression, or suppression, is contemplated in the State Medical Service which Government proposes to form in England.)

In conclusion, if the Colonial Medical Service were permitted to develop on democratic lines it would render an excellent account of itself.—I am, etc.,

F. M. PURCELL, M.D., F.R.C.P.I., D.T.M.&H.

Council of the R.C.S.

SIR,—Latterly the Council of the Royal College of Surgeons of England has shown its desire to make itself more representative of the many facets of British surgery, and many Fellows and Members of the College appreciate its recent action in co-opting one of the Members to be present at its deliberations (*B.M.J. Supplement*, Aug. 5, p. 31). As opposed to this liberal action, however, it is unfortunate that, previous to its recent election, the Council circulated to the Fellows (who are the electors) a note to the effect that it deprecated canvassing for the election "whether personally or by institutions or associations." Such a ban, if obeyed, is likely to have far-reaching effects on the constitution of the Council, for although most Fellows regard personal canvass with distaste, yet "group canvassing" for the purpose of securing adequate representation of the various specialties of surgery, as well as provincial and other types of geographical representation, is essential if a widely scattered electorate of some 2,500 Fellows is to unite for the purpose of building up a Council representative of the many interests involved.

Formerly, the Council was representative almost solely of London surgery, with only an occasional representative of the Provinces; but under the influence of Moynihan provincial surgery received its due recognition, and this was reflected in the composition of the Council, which for some years has had about one-third of its members drawn from provincial schools. This has only been achieved, however, by the combined action of a group representing the provincial medical schools seeking to secure representation of these more or less isolated bodies. The standing of the great London medical schools, with their traditions and loyalties, places them in such a strong position in this election that to deny such a canvass to the smaller London schools and the provincial schools inflicts a real hardship and practically excludes them in future from the probability of adequate representation. Even under circumstances operative until recently, it is notable that, in 1942, while one London hospital had four surgeons on the Council at that time three provincial schools were unrepresented.

The Council has no power to enforce such a ban, and by its imposition places itself in an invidious position by seeking to withhold from its scattered electorate one of the means by which the various interests involved may come to a decision as to their representation. If, as I believe it does, the Council wishes to make itself representative of British surgery in the widest possible sense, it should welcome among its Fellows all reasonable activities to promote this end and not seek to guide them too zealously.—I am, etc.,

Birmingham. SEYMOUR BARLING.

Wet Babies

SIR,—An obvious fallacy under the heading "The Crying Baby" in Dr. Doyne Bell's lecture printed in your issue of July 29 almost prevented my reading the text of an instructive article.

Surely the treatment for a hot baby and a wet pillow is a dry pillow and a less hot baby—and incidentally the consoling presence and touch of the baby's mother. Is it not the exception to find any abnormality on examination when the mother complains of her baby crying? Seldom has she troubled to find out whether the baby is thirsty, hungry, too hot or too cold, or only frightened.

May I suggest that a common cause of "momentary discomfort" is a full bladder? Some time ago a midwife said to me that a baby never passes water in his sleep. The assertion surprised me at the time, but I have since demonstrated its truth in the case of one baby. The very young baby wakes and cries at the discomfort, and can often be picked up before passing water, with the early establishment of some degree of control. More important, the baby is reassured, comfortable, and will settle happily to sleep until the time of the next feed. The use of sedatives can only inhibit this natural phenomenon. Six months is an early age at which to take drugs for non-pathological conditions and as a substitute for human contact.—I am, etc.,

Zennor, Cornwall. S. M. HALLIDAY.

Tie the Cord

SIR,—I have been interested in the recent correspondence under the heading of "Why Tie the Cord?" in the *Journal*, and a recent tragic experience has convinced me more than ever of the necessity for tying the cord.

Within the past six weeks I delivered a patient spontaneously of a living child at 11 p.m. When delivering the child I remarked on the extreme thickness and gelatinous nature of the cord, and, as a result, tied the cord in three places, using triple reef-knots firmly tied. Just over one hour later I examined the child and all was well, and I left the nursing home. One and a half hours later I was called back urgently to the home because the child had had a very severe haemorrhage from the cord, from which it died some three hours after delivery and before transfusion could be instituted. Examin-

tion showed that the cord had contracted down considerably, and that haemorrhage had occurred through the umbilical vessels. Not one of the ligatures had cut through the vessels, and the haemorrhage appeared to be due entirely to the fact that the ligatures became relatively loose due to the contraction within the cord.

While undoubtedly it may be unnecessary to tie the cord in some cases, I think a case such as this demonstrates the fact that not only should the cord be tied in every case but that it should be tied very securely indeed, and, most important, that it should be watched carefully for some hours afterwards.—I am, etc.,

London, W.1. CHARLES D. READ.

W.C. Equipment

SIR,—Is it not time that lavatories be fitted with adequate facilities for washing oneself after defaecating, following the example of the French bidet? The use of toilet paper is insufficient for scrupulous cleanliness, and it probably has a local irritant action on the delicate muco-cutaneous junction of the anus. Tiny excoriations and fissures produced in this way are liable to infection. It would be an advantage if some soft and absorbent material could be used instead of toilet paper.—I am, etc.,

G. A. POWELL-TUCK.

The Young Married Doctor

SIR,—I think I am speaking for a large section of the younger members of the profession, who, owing to war service, have already been separated for a considerable time from their wives, when I say that there are many of us who, although desirous of continuing an interrupted hospital career when we return, feel we will be forced to deny ourselves this owing to the anomalous situation that still obtains, which makes it impossible for junior hospital appointments to be held by married men who wish to continue to live with their families.

It seems that the hospitals will be deprived of the services of many who aspire to specialist work, who, on the above account, have been forced to forgo their ambition. Would it not be fair to these men if some consideration were given to this problem; that, if married quarters cannot be provided, at least permission might be extended to facilitate their lodging in the close neighbourhood of the hospital with telephone communication?—I am, etc.,

TOM BARNS.

Early Days at Johns Hopkins

SIR,—I have read with interest your leading article in review of the *Chronicles of the Johns Hopkins Hospital*, and in reading I missed the name of one brilliant son. Early in 1901, when on my first visit to the United States, I had the delightful privilege of dining with Prof. Osler and meeting at his table his distinguished colleagues, Halsted, Welch, and Howard Kelly. Among those present was a young surgical resident, Harvey Cushing, whose star in course of time was to give added lustre to the university and to the brilliant constellation of the "Big Four" of Sargent's portrait.—I am, etc.,

London, W.1. C. GORDON-WATSON.

The annual report for 1942 of the Palestine Department of Health states that the birth rate was the lowest yet recorded. The infant mortality rate was higher, especially in the towns, than that of the previous year; but the general death rate was lower. There were five cases of plague—three of them infected in Haifa, in Northern Palestine, and fifteen in Jaffa and Tel Aviv, the first outbreak in this area since 1924. A few cases of smallpox were attributable to infection brought in from Syria and Lebanon, where the disease was prevalent; and a sharp outbreak occurred in the Tulkarm district, caused by returning pilgrims from Mecca. Land quarantine was imposed, and 270,000 persons were revaccinated within four months. The year 1942 showed the highest incidence of enteric fever since the British occupation: 4,065 cases were notified with 373 deaths. It is suggested that two factors played a leading part in the spread of the disease: military requirements caused unusual movements of labour; and, as a result of the high cost of living, much food was eaten which in normal times would have been regarded as unfit for human consumption. In all, 178,000 persons received protective inoculations, and the authorities hope to extend this measure.

Obituary

JOHN DODDS PRICE, M.R.C.S.

Dr. John Dodds Price died at Ferring, Sussex, after a painful illness, aged 79. He studied medicine at Guy's Hospital and qualified M.R.C.S., L.R.C.P. in 1889. A large part of his professional life was spent in India. After his return to England Dr. Dodds Price, who had joined the British Medical Association a year or two after qualifying, served on the Council in 1926 and 1927, and also for two years on the Dominions Committee and two of its subcommittees.

Sir LEONARD ROGERS, F.R.S., writes:

May I pay a brief tribute to my old friend Dr. John Dodds Price, who died on Sept. 1. Very soon after qualifying he went out to work on tea estates in the Bengal Duars and a little later took up similar work in the Nowgong District of Assam, where he completed nearly 35 years' service in India before retiring. He rendered me invaluable help during my investigation of kala-azar in Assam in 1896–7, and it was his earlier action in placing newly recruited coolies on badly infected tea gardens in newly constructed lines a short distance from infected ones that gave me the clue to the disease being a house or site infection. He also demonstrated the value of demolishing infected lines and moving the healthy coolies alone to new ones, in stamping out the disease from a number of tea estates in the Nowgong district and saving the industry in that district from ruin, as recorded in a joint paper of ours published in the *British Medical Journal* of Feb. 7, 1914. During the war of 1914–18 he acted as civil surgeon of the Nowgong District in addition to his other work, and so great was his professional reputation that he was awarded a Kaisar-i-Hind Medal of the first class.

In addition to being a much-beloved medical practitioner John Dodds Price was a great sportsman and rode in amateur steeplechases in his bachelor days, and later became captain of his district polo team. When a boy he sang in Westminster Abbey and was trained as a tenor, but felt a musical career too hazardous because his mother was dependent on him. He was thus an all-round man, but a most modest one, who will be greatly missed by his many friends. After his retirement he was much crippled by progressive osteo-arthritis of one hip-joint, but bore his troubles bravely. He leaves a widow, a son, and a daughter to mourn his loss.

HARVEY FRANCIS, M.D., died at his home in Woodthorpe, Nottingham, on Aug. 4, at the age of 75, after a lengthy illness, borne with the fortitude, courage, endurance, and selflessness which had been his character through life. His medical education was at Durham University and St. Mary's Hospital, where he held the posts of resident obstetric officer and house-surgeon. For 47 years he practised at Arnold, on the northern outskirts of Nottingham. His practice was an extensive and varied one, comprising miners, shopkeepers, business men, and landed gentry: with all alike he was deservedly popular. He possessed a most attractive personality, always cheery, always helpful when serious trouble came, so that his patients learned not only to love him but to put in him the most complete confidence. He was a keen and conscientious worker, and right up to the time of the onset of his illness he continued to carry on his work with the same energy and devotion which he had always given. In addition to his large private practice Dr. Francis held many appointments, including those of M.O.H. to the Arnold Urban District Council, which post he held for 40 years, and that of certifying factory surgeon. During the war of 1914–18 he was in medical charge of the Arnot Hill Hospital, Arnold, a hospital of fifty beds. His services to this hospital, so devotedly given, were recognized by the award of the O.B.E. His loss will be severely felt by his fellow practitioners in Nottingham and Notts, with all of whom he was deservedly popular. A keen cricketer in his early years, he frequently played for the local cricket club, and in his later years often attended the Notts County Cricket Club matches at Trent Bridge. He leaves a widow, three sons, and a daughter. Two of his sons were with him in partnership, the elder of whom is now carrying on the practice, the other serving as flight lieutenant in the R.A.F. in Italy. To them all we extend our sympathy.—W. R.

We regret to announce the death at his home in London on Aug. 8 of Dr. HENRY CARSON SMYTH. Qualifying in Dublin in 1911, his early professional life was spent in Ireland. He is still vividly remembered by old colleagues of Steevens's Hospital, where he was resident surgeon. He was liked by

all the students, and he displayed a lively interest in their work. In the mess he showed his wide general knowledge of the sciences, continually putting pointed and stimulating questions to his juniors. A colleague writes: Dr. Smyth's professional interests were wide, but he made a special study of venereal disease and dermatology. Some of his work is displayed in two papers on the use of salvarsan. In the last war he was civil surgeon at the Royal Military Infirmary and Portobello Military Hospital in Dublin. Later he served as captain, R.A.M.C., in Malta and Salonika, where he met Dr. Janet Park Walton, whom he married, and who has, especially in the final years of failing health, given him great assistance in his work. In 1918 Dr. Smyth settled down with his wife in general practice in Coldharbour Lane, London, where he soon became widely known and popular, and where he practised for twenty-six years. He was a member of the B.M.A. and a Fellow of the London Dermatological Society. All his spare time he devoted to the work of the St. John Ambulance Brigade, to which he was divisional surgeon, being lecturer and examiner for South London. He was an enthusiastic Freemason. Harry Smyth had a keen sense of humour, which helped to endear him to his patients, who often came to him for friendly advice as well as for medical attention. He was loved by children and animals, with whom there speedily sprang up mutual understanding and affection. Many of the people of Loughborough Junction and Herne Hill, to which he extended his practice in 1928, have cause to mourn the passing of a beloved physician and friend.

Dr. GUY FOSTER BARHAM, late medical superintendent of Claybury Mental Hospital, died on Aug. 30 at Gorran Haven, Cornwall. He began the study of medicine at Cambridge University, taking his B.A. in 1895, and went on to the London Hospital, qualifying M.R C.S., L.R.C.P. in 1901. He graduated M.B. at Cambridge in 1903 and proceeded M.D. in 1912. He was for a time house-surgeon at the Poplar Hospital and started his career in psychiatry at the London County Mental Hospital, Long Grove, where he was serving as senior medical officer at the time when the L.C.C. appointed him to be chief of Claybury Hospital. Dr. Foster Barham was a member of the Royal Medico-Psychological Association; he joined the B.M.A. in 1918 and served for six years at headquarters on the committee appointed by the Council to consider lunacy law and mental disorders. He published papers in the *Journal of Mental Science* and in the *Archives of Neurology and Psychiatry*.

Dr. WILLIAM MARTIN FROBISHER, who had practised for over 50 years in Leeds, died in retirement at Headingley on Aug. 30. He was a descendant of Sir Martin Frobisher, the famous 16th century navigator. He studied medicine at Leeds and took the M.R.C.S. diploma in 1897; before settling in practice he held a house appointment at the General Infirmary at Leeds. His elder son, Dr. J. H. M. Frobisher of Forest Row, Sussex, served in the R.A.M.C. both in the last war and in this war, retiring with the rank of major.

Dr. WILFRID LOUIS REMI FLEMING, formerly chairman of the Guildford Division of the B.M.A., died at Pirbright, Surrey, where he had practised for a long time. The son of Andrew Fleming, of Kilmarnock, he studied medicine at Westminster Hospital and took a course in obstetrics at the Rotunda Hospital, Dublin, qualifying M.R.C.S., L.R.C.P. in 1895. Before settling in general practice Dr. Fleming was house-surgeon and resident obstetric assistant at the Westminster and house-physician at the Bethlem Royal Hospital. During the last war he served as medical officer at Henley Park Auxiliary Military Hospital; later he was for a time M.O. to the Bisley Farm School and Shaftesbury Home. A man with a strong sense of public duty, he was a justice of the peace for the county of Surrey and chairman of the managers of the Pirbright elementary schools. Dr. Fleming joined the B.M.A. in 1900 and was also a member of the Royal Medico-Psychological Association.

The death is announced of Dr. ALBERT PENARD LAYCOCK, who before settling in general practice in South-West London had spent ten years as a medical missionary. He was born at Versailles on Sept. 26, 1877, son of the Rev. J. M. Laycock, and had his early education at Plymouth College, Merchant Taylors School, and Monkton Combe School. Entering St. John's College, Cambridge, he took his B.A. (with first-class honours in the Natural Sciences Tripos) in 1898, and went on to the London Hospital, qualifying M.B., B.Ch. in 1902. He was then for a time superintendent of the St. Pancras Medical Mission until he joined the China Inland Mission, Changsha, Lanchowfu, in 1905. While working there he was for two years surgeon to the Chinese Imperial Maritime Customs. He died on Sept. 5 in Sherbrooke Road, Fulham.

The Services

Col. R. Hay, C.I.E., I.M.S., has been appointed an Honorary Physician to the King in succession to Col. H. E. Shortt, C.I.E., retired.

Major (Temp. Lieut.-Col.) J. A. Chapel, R.A.M.C., Reserve of Officers, has been appointed M.B.E. (Military Division) in recognition of gallant and distinguished services in the field.

CASUALTIES IN THE MEDICAL SERVICES

Killed in action.—Lieut. Robert Russell Waddell, R.A.M.C.

Missing, presumed killed.—Temp. Surg. Lieut. William Hamilton Cassels Donald, R.N.V.R., Surg. Lieut. Derek Napier McKenzie, R.A.N.V.R.

Died on active service.—Major Charles Peter Mann, R.A.M.C.

Died.—War Subs. Capt. Benjamin David Berger, R.A.M.C.

Wing Cmdr. WILLIAM MILLIGAN died on Sept. 3 while serving on an R.A.F. headquarters over-seas. He was born in May, 1902, studied medicine at Leeds University, and qualified M.B., Ch.B., M.R.C.S., L.R.C.P. in 1927. He entered general practice, and on Dec. 28, 1937, was commissioned as flying officer in the Medical Branch of the R.A.F.V.R. After his embodiment for war service on Sept. 30, 1939, Wing Cmdr. Milligan served at various stations at home, and in 1943 was posted to command a station hospital.

DEATHS IN THE SERVICES

The death is reported of Major-Gen. Sir ERNEST ALEXANDER WALKER, I.M.S., K.C.I.E., C.B., at Duncan, British Columbia, in the age of 63. Son of the Rev. A. Walker, senior Army Chaplain Church of Scotland, he was educated at the Forfar Academy and Edinburgh University and graduated M.B., Ch.B. with honours in 1901, took the M.D. in 1940 and the F.R.C.S.Ed. in 1912. He entered the Indian Medical Service in 1902, and during the war of 1914–18 he served in Iraq in 1915–16, was taken prisoner at Kut-al-Amara, and was twice mentioned in dispatches. In 1920–1 he was D.A.D.M.S. (Mobilization), was promoted to be Deputy Director of Medical Services in 1929, was appointed to the medical charge of the Eastern Command, India, in 1933, and succeeded to the Director-Generalship of Medical Services, India, in 1933, where he proved to be a capable administrator. He became Honorary Surgeon to the King in 1932, and a C.B. in 1934. He retired in 1937 and in the following year was made a K.C.I.E. for his long and distinguished service on the military side of the I.M.S. General Walker had published papers on various technical medico-military subjects. Among his recreations were shooting and fishing.

Dr. Ernest Jones writes: The death in India of Lieut.-Col. OWEN BERKELEY HILL, I.M.S., recently announced will cause grief to a wide circle of friends, to whom his kindly loyalty, exhilarating companionship, characteristic drollery and wit, had endeared him. He will be remembered in India as the institutor of valuable reforms during the eighteen years in which he directed the European Mental Hospital at Ranchi, and as a pioneer in introducing modern psychology into that country. His work in mental hygiene, in which field he represented India in several international congresses, was also noteworthy. A certain intolerance of officialdom, manifested by a stream of saucy—though never malicious—retorts, greatly diminished the influence his progressive outlook might otherwise have had among the powers that be. He published a volume of psychiatric essays, dealing especially with the ethnology of Indian peoples, and a racy autobiography.

Universities and Colleges

UNIVERSITY OF SHEFFIELD

At its meeting on Sept. 8 the University Council received the resignations by (1) A. Rupert Hallam, M.D., of his post of lecturer in dermatology; (2) P. E. H. Howarth, M.B., Ch.B., and R. E. Peasegood, M.B., Ch.B., of their posts of temporary demonstrators in anatomy. The Council accepted the resignations with regret, and accorded its thanks to Dr. Hallam, Mr. Howarth, and Mr. Peasegood for their services to the University.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

Two lectures, under the auspices of the Imperial Cancer Research Fund, will be delivered by Prof. W. E. Gye, M.D., F.R.S., at the College, Lincoln's Inn Fields, W.C., on Thursdays, Oct. 5 and 12, at 4 p.m. His subject is "The Part played by Viruses in Cancer Causation." The lectures are open to medical practitioners, scientists and advanced students.

No. 35

INFECTIOUS DISEASES AND VITAL STATISTICS

We print below a summary of Infectious Diseases and Vital Statistics in the British Isles during the week ended Sept. 2.

Figures of Principal Notifiable Diseases for the week and those for the corresponding week last year, for: (a) England and Wales (London included). (b) London (administrative county). (c) Scotland. (d) Eire. (e) Northern Ireland.

Figures of Births and Deaths, and of Deaths recorded under each infectious disease, are for: (a) The 126 great towns in England and Wales (including London). (b) London (administrative county). (c) The 16 principal towns in Scotland. (d) The 13 principal towns in Eire. (e) The 10 principal towns in Northern Ireland.

A dash — denotes no cases; a blank space denotes disease not notifiable or no return available.

Disease	1944 (a)	(b)	(c)	(d)	(e)	1943 (Corresponding Week) (a)	(b)	(c)	(d)	(e)
Cerebrospinal fever	27	—	22	—	—	43	5	20	2	
Deaths		—	—				1	1		
Diphtheria	445	6	147	88	15	625	35	174	92	19
Deaths	4	—	—	2	—	9	1	4	2	1
Dysentery	419	27	93	—	1	238	12	136	—	—
Deaths				—	—				—	—
Encephalitis lethargica, acute	1	—	—	—	—	4	1	—	—	—
Deaths		—					1			
Erysipelas			49	8	2			32	5	—
Deaths		—					—			
Infective enteritis or diarrhoea under 2 years				197					98	
Deaths	63	8	57	21	9	69	13	12	20	14
Measles*	1,669	27	65	39	16	674	37	31	8	3
Deaths	—	—	—	2	—	2	—	1	—	1
Ophthalmia neonatorum	59	2	20	—	—	91	2	19	—	—
Deaths										
Paratyphoid fever						14	—	2	—	—
Deaths						—	—	—	—	—
Pneumonia, influenzal*	297	13	5	—	2	304	18	5	2	—
Deaths (from influenza)	5	—	—	1	—	7	—	1	—	1
Pneumonia, primary			150	15				148	10	
Deaths		13		4	4		17		10	6
Polio-encephalitis, acute	7	1				1	—			
Deaths		—					—			
Poliomyelitis, acute	25	—	22	1	1	16	1	1	2	—
Deaths		—					—			
Puerperal fever		1	6		—		3	14		—
Deaths										
Puerperal pyrexia‡	132	2	10	3	3	171	8	14	1	4
Deaths		—					—			
Relapsing fever	—	—			—	—	—			—
Deaths										
Scarlet fever	1,137	28	204	21	45	2,206	221	331	48	75
Deaths	1	—	1	—	—	—	—	—	—	—
Smallpox	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Typhoid fever						11	1	5	10	3
Deaths						3	—	—	—	1
Typhus fever	—	—	—	—	—	—	—	—	—	—
Deaths				—	—				—	—
Whooping-cough*	1,389	44	61	82	11	1,928	108	266	59	26
Deaths	2	2	1	2	—	8	—	5	3	—
Deaths (0–1 year)	305	23	109	39	25	295	33	54	37	35
Infant mortality rate (per 1,000 live births)										
Deaths (excluding still-births)	3,649	414	569	170	106	3,504	482	480	177	118
Annual death rate (per 1,000 persons living)			13·1	11·0	§			10·8	11·6	§
Live births	6,167	410	822	339	227	5,959	718	904	391	271
Annual rate per 1,000 persons living			16·7	22·0	§			18·5	25·7	§
Stillbirths	216	12	23			191	22	26		
Rate per 1,000 total births (including stillborn)			27					28		

* Measles and whooping-cough are not notifiable in Scotland, and the returns are therefore an approximation only.

† Includes primary form for England and Wales, London (administrative county), and Northern Ireland.

‡ Includes puerperal fever for England and Wales and Eire.

§ Owing to evacuation schemes and other movements of population, birth and death rates for Northern Ireland are no longer available.

EPIDEMIOLOGICAL NOTES

Discussion of Table

In *England and Wales* the incidence of dysentery, whooping-cough, scarlet fever, and diphtheria rose by 120, 73, 66, and 35 respectively. There were 45 fewer cases of measles reported than last week.

The returns for whooping-cough in Gloucestershire rose by 39. Measles notifications decreased in most areas of the country, but Lancashire had 55 more cases than last week, and Northumberland 56.

A new wartime record for dysentery was set up during the week, when 419 cases were notified. The cases occurred over a wide area, and fifteen counties recorded 10 or more cases. The largest centres of infection were Surrey 46, Sussex 35, Buckinghamshire 31, London 27, Essex 27, Glamorganshire 25.

In *Scotland* there were 13 more cases of diphtheria than last week, making the third consecutive week for which an increase has been reported. Notifications of acute primary pneumonia went up by 42 and those of scarlet fever by 25. There were 22 fewer cases of dysentery, the largest returns being Glasgow 39, and Edinburgh 23. The number of deaths from gastro-enteritis rose sharply during the week, and 53 of the total of 57 occurred in Glasgow. Deaths for the corresponding week last year numbered 12. The source of the infection is unknown, but as a precaution the M.O.H. has advised the use of dried milk for infant feeding.

In *Eire* the high level of notifications for diarrhoea and enteritis was still further increased; 151 of the 197 cases were notified in Dublin C.B. The rise of 52 cases in whooping-cough was due mainly to an outbreak in Clare, Tulla R.D. 30.

In *Northern Ireland* a small rise of 18 occurred in the notifications of scarlet fever.

Week Ending September 9

The notifications of infectious diseases in England and Wales during the week included: scarlet fever 1,251, whooping-cough 1,223, diphtheria 481, measles, 1,138, acute pneumonia 303, cerebrospinal fever 41, acute poliomyelitis 24, dysentery 622, paratyphoid 3, typhoid 7.

Correction

In last week's table the dysentery notifications for Scotland were given as 15. The figure should have been 115.

Medical News

It has been decided that the programme for the 1944 annual meeting of the Faculty of Radiologists must be curtailed owing to prevailing conditions. The meeting will be held at the Royal College of Surgeons, Lincoln's Inn Fields, on Friday, Sept. 29, beginning at 10 a.m. There will be a discussion on the Government White Paper on a National Health Service at 2.30 p.m.

The 236th meeting of the Biochemical Society will be held in the Department of Biochemistry, University, Western Bank, Sheffield, on Friday, Sept. 29, at 11 a.m.

A meeting of the Association of Clinical Pathologists will be held on Saturday, Sept. 30, at the London School of Hygiene and Tropical Medicine, Keppel Street, W.C. Programme: 11 a.m., Prof. A. A. Miles and Dr. Nancy Hayward, the specificity of the Nagler reaction and the general problem of wound bacteriology; 12 noon, Air Cdre. T. C. C. Morton, investigation of a case of eosinophilia from the Tropics (with demonstrations); 2 p.m., Sir Alexander Fleming, the laboratory control of penicillin therapy (with demonstrations); 3 p.m., (*a*) Lieut.-Col. Yale Kneeland, U.S.A.M.C., experiences with penicillin in infectious diseases, (*b*) Col. D. M. Pillsbury, U.S.A.M.C., penicillin in the treatment of venereal disease; 3.50 p.m., Lieut.-Col. J. S. Jeffrey, R.A.M.C., commentary on Sir H. W. Florey's film on the treatment of war wounds with penicillin. Demonstration (on view 10 a.m. to 5 p.m.), Major J. Edwards, U.S.A.M.C., a case of coccidioidomycosis immitis.

The first lecture in the autumn programme of the 32nd annual series of Chadwick Public Lectures is to be delivered on Tuesday, Oct. 3, at 2.30 p.m., at the Royal Society of Tropical Medicine and Hygiene, 26, Portland Place, W., when Lord Amulree, M.D., will lecture on "Water Supplies in Peace and War." Admission to all the Chadwick lectures is free; tickets are not required.

The following medical films will be shown at the Solarium, Grange Road, Bermondsey, S.E.1, at 8.30 p.m. on Tuesday, Oct. 3, "Highland Doctor," "Blood Transfusion," and "Scabies." Any doctors wishing to attend will be welcome. No. 1 bus to Grange Road.

The North-West London Branch of the English New Education Fellowship will hold a meeting on Tuesday, Oct. 3, at 7.45 p.m., when Drs. S. W. Jeger and R. W. Cockshut will discuss schools and the State Medical Service. The meeting is open to the public without charge, and will take place in the School Hall, Hendon County School, Golders Rise, Hendon.

The National Council for Mental Hygiene has arranged a course of ten lectures on "The Psychology of Frustration and Fulfilment in Adult Life," to be held in London and repeated in Birmingham. The London series will be given at Caxton Hall, S.W.1, on Tuesdays at 5.30 p.m. from Oct. 3 to Dec. 5. The Birmingham series will be given at Friends' Meeting House, Bull Street, on Wednesdays at 5.30 p.m. from Oct. 4 to Dec. 6. The fee for a complete course is £1; single tickets, so far as accommodation permits, 3s. 6d., obtainable at the hall before each lecture. Application for tickets for a course should be sent to the Secretary, National Council for Mental Hygiene, 39, Queen Anne Street, London, W.1, or to Messrs. Dale, Forty and Co. Ltd., 80, New Street, Birmingham, 2, who are acting as agents for the Birmingham course.

The annual general meeting of the Association of Industrial Medical Officers will take place at the London School of Hygiene, Keppel Street, W.C., on Saturday, Oct. 14, at 11 a.m. Morning session, 11 to 1, private business. Afternoon session, commencing 2.30 p.m., an address by Prof. John A. Ryle, M.D., "Social Medicine as a Discipline."

At a sessional meeting of the Royal Sanitary Institute to be held in the Perrymount Cinema, Haywards Heath, on Saturday, Oct. 14, at 10.30 a.m. a discussion on "Diphtheria Immunization" will be opened by Dr. W. B. Stott, M.O.H., Cuckfield Rural District Council.

At the Odeon Cinema, Plymouth, on Sunday, Oct. 15, at 11 a.m., a British Council medical film, "Surgery of Chest Diseases," will be shown. All medical practitioners, including British and Allied Services, are welcome. Address by Surg. Rear-Adml. G. Gordon-Taylor.

Chevrons for war service and wound stripes are to be awarded to volunteer stretcher-bearers enrolled at hospitals in the E.M.S.

Letters, Notes, and Answers

All communications with regard to editorial business should be addressed to THE EDITOR, BRITISH MEDICAL JOURNAL, B.M.A. HOUSE, TAVISTOCK SQUARE, LONDON, W.C.1. TELEPHONE: EUSTON 2111. TELEGRAMS: *Aitiology Westcent, London.* ORIGINAL ARTICLES AND LETTERS forwarded for publication are understood to be offered to the *British Medical Journal* alone unless the contrary be stated.

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B.M.A. SCOTTISH OFFICE: 7, Drumsheugh Gardens, Edinburgh.

ANY QUESTIONS?

Chinosol

Q.—*What are the present opinions on and uses of "chinosol," now known as hydroxyquinoline sulphate? When I was in practice I used it continuously for all minor surgical cases, and found it very satisfactory. Primary union of stitched wounds I looked upon as a certainty. It is quite non-irritating in any strength. Its disadvantage is that it attacks instruments. Is chinosol out of favour now? If so, why?*

A.—Chinosol has a strong antiseptic but little rapid germicidal action, which is exerted mainly against Gram-positive cocci; Gram-negative organisms are much less susceptible. Solutions are acid, and it has therefore some local irritant action, but is certainly less toxic than many other commonly used antiseptics. So far as this country is concerned chinosol cannot be said to have fallen out of favour, for the simple reason that it has never come into use to a sufficient extent for the reverse process to be noticeable. There is no evidence in the literature of diminished popularity in the country of its origin: German papers in comparatively recent times describe its use for the treatment of wounds, infections of the skin, eye, and female genital tract, for throat carriers of *C. diphtheriae*, and for a variety of purposes in veterinary medicine. Without practical experience of its use no precise judgment of its merits or comparison with other antiseptics is perhaps justifiable. It may nevertheless be pointed out that chinosol has now some very formidable rivals. The newer acridine compounds are more powerful antiseptics, sulphonamides applied locally have a well-attested antiseptic actio and are almost completely non-toxic, while penicillin combines bo virtues in the highest degree.

Dangers of Screening and Radiography

Q.—*How frequently can a patient have ordinary straight x-ra plates of the chest with a full-size x-ray machine, assuming th ordinary exposures are used—i.e., weekly, fortnightly, monthly, o what? My interest lies in the management of artificial pneum thoraces, where treatment and control may go on for five years o more. What are the short- and long-term ill effects due to ove exposure to these x rays? Is regular screening likely to be les cumulative than regular x-raying?*

A.—Under normal working conditions the use of radiology fo the control of the management of artificial pneumothorax does no give rise to any anxiety about either local or general effects o radiation on the patient. The initial period may require severe examinations within a few days, but after this the intervals gradual increase. If radiography or screening is employed to direct th cutting of adhesions, or tomography used for the visualization o location of cavities, then due allowance must be made for th additional exposure. While it is difficult to imagine a case in whic a weekly radiograph may be necessary over a period of years, th too may be carried out without anxiety should real necessity arise.

Screen examinations are a different proposition. Presuming a interesting case, much more time may be spent screening than mu be realized, and the quantity of radiation received by the patie may be considerable and uncertain. However, an experienc observer, knowing his cases, may secure the information he desir in a few seconds. Otherwise the patient would probably recei more radiation during average screening than in one exposure fo a radiograph.

The ill effects from one dose over-exposure are local: inflamm tion, alopecia (temporary or permanent), vesication, ulceration, an ultimately, possibly local malignancy—in that order and dependin upon the degree of overdose. If the area is large there will b sepsis, toxaemia, and much pain. The ulceration may not hea and skin grafts may be necessary to repair. The lesser degrees o damage may result later in skin and glandular atrophy, telangiectase and late ulceration. The cumulative effect of long-continued sma doses locally gives rise to skin and glandular atrophy, telangiectasi fissures, and warty growths that may go on to malignancy an metastasis.

General body irradiation such as may be received by those practi ing radiology under unfavourable conditions, or carelessly unde favourable conditions, may give rise to leucopenia, which i unchecked may lead to sterility and a fatal anaemia. Some peopl are more susceptible than others, and there is also reason to believ that, in some, minimal body irradiation under similar condition gives rise to an increase in the red cell count before the white i recognizably altered.

The difference in the quality of the radiation (wave-length) a used in radiography and screening of the chest is such that it is no an important factor in the question under consideration, but th radiographic dose can be calculated precisely. The screening dos may be of a very varying magnitude under different conditions an in different hands.

With regard to protection, reference should be made to the repo under the heading "Protection against *X* Rays" in the *Journal* o April 1, 1944 (p. 480), and to the recommendations of the Britis *X*-ray and Radium Protection Committee, which may be obtaine free on application to the General Secretary, British Institute o Radiology, 32, Welbeck Street, London, W.1. See also the articl "Effects of Radiation on Workers," by Ralston Patterson, *Britis Journal of Radiology*, January, 1943, p. 3.

Blood-pressure Readings

Q.—*What is now generally accepted as being the correct metho of ascertaining the diastolic blood pressure? Should the reading be taken when the character of the sound changes from slapping t a softer, more prolonged note, or when finally no sound at all ca be heard? Is it now generally accepted that the diastolic pressur is of greater significance than the systolic in cases of suspecte arteriosclerosis? Does the diastolic pressure tend to vary as greatl as does the systolic at different times in the same individual? Wha may be taken as the normal range of diastolic pressures in me aged from 20 to 60?*

A.—The following recommendations for determining the diastoli blood pressure are contained in the joint report of the Cardia Society for Great Britain and Ireland and the American Hea Association (*Brit. Heart J.*, 1939, **1**, 261): "The patient should b allowed time to recover from any recent exercise or excitement. . . Auscultation should be conducted during slow deflation. . . . T point where the loud clear sounds change abruptly to the dull muffl sounds should be taken as the diastolic pressure." It is impossi to be dogmatic about whether the systolic or the diastolic pressu

has the greatest significance in arteriosclerosis. Severe arteriosclerosis of the aorta tends to lower the diastolic pressure, whereas in early essential hypertension the rise in blood pressure may be evident only in the diastolic reading. The percentage fluctuation of the diastolic pressure is as great as that of the systolic in hypertensive patients, but in health a specific stimulus may have a different effect on the systolic and diastolic pressures. For instance, vigorous exercise often causes a rise in the systolic pressure while the diastolic pressure remains the same, or falls. The best statistics for the blood pressure in healthy individuals are those given by Symonds (*J. Amer. med. Ass.*, 1923, **80**, 232). According to him the range of the diastolic pressure at 20 years is 76 to 85 mm. Hg, and at 60 years 82 to 90 mm. Hg.

Acne

Q.—What is a simple and practical form of treatment for acne where large numbers of not very intelligent young people are concerned?

A.—Acne has two complementary and essential factors—an endocrine imbalance and a seborrhoeic skin. A 2% sulphur and salicylic acid ointment modifies the seborrhoeic fraction: it can be applied at night. Treatment on these lines is eventually successful by modifying one of the essential components.

Headache of Acromegaly

Q.—Can anyone suggest something to relieve the headache of acromegaly or of a ? pituitary tumour causing the symptoms? I have tried most of the usual analgesics without any effect. The condition of the patient is distressing to behold, and one feels so helpless.

A.—If a pituitary tumour is present, as might be indicated by optic atrophy or an enlarged sella turcica, operation should be considered, or, alternatively, radiotherapy. If there is no tumour, symptoms might be relieved by testosterone or stilboestrol, both acting by inhibiting the activity of the pituitary and possibly diminishing its turgescence or size. In an attempt to get a decisive response, large doses should be used—e.g., 50 mg. intramuscularly daily of testosterone or 5 mg. of stilboestrol. Later on methyl testosterone by mouth or stilboestrol by mouth could be tried.

Home-made Penicillin

Q.—Although Penicillium notatum is supposed to be a common mould, I cannot find out where to obtain a pure culture. What is the composition of the best culture medium obtainable by purchase, and where can it be bought? I have failed to get any from three laboratories. I wish to use a home-made culture of Penicillium notatum as a local application in gonorrhoea in a girl of 6 who is sulphathiazole-sensitive (granulocytopenic), who has been benefited but not cured by sulphathiazole, and whose mother is 7 months pregnant. I propose to inject the liquid culture into the vagina instead of using pot. permang. lotion. Why should not this culture in liquid be used as a local application until the supply of penicillin is abundant? I have an incubator.

A.—*Penicillium notatum* is obtainable from the National Collection of Type Cultures, Lister Institute, Elstree, Herts. For methods of preparing crude culture filtrate for local treatment the questioner is referred to a recent article by J. M. Alston in this *Journal* (May 13, 1944, p. 654). We know of no commercial source from which the necessary culture medium can be bought. An ordinary incubator will not serve for this purpose: the temperature required is 24° C. A good deal of other equipment and considerable knowledge are necessary for the production of a filtrate of known and adequate potency, and despite recent claims which have been made for the possibilities of home-made penicillin, the pitfalls involved are so numerous that it cannot be recommended for any serious therapeutic undertaking such as in the case described.

Clicking Mandible

Q.—My commanding officer has recently developed a very audible clicking of the mandible in the left temporo-mandibular joint. It occurs only when he is eating, and he can demonstrate it by "chewing the cud," as he puts it. It is becoming an increasing source of embarrassment to him, for his fellow officers imagine he has a loose denture. He has dentures, but they fit perfectly and are not the cause of the noise. He is aged 50, full-faced and rotund. Could you advise me on the best treatment for such a condition?

A.—Clicking in the temporo-mandibular joint may be either bony or cartilaginous. In the former instance the cause is usually an arthritis of the joint, in the latter an abnormal or loose interarticular fibrocartilage. The treatment of the arthritic variety is along the usual lines which are adopted for arthritis elsewhere, but on the whole the results are disappointing. Sometimes the dentist can help by building up the "bite" posteriorly, so preventing too close closure of the jaws and thus relieving the joint surfaces. In cases such as the present one, where a denture is worn, it is particularly important to see that the "bite" is correct, as an incorrect "bite" may not only be a causative factor in the production of the arthritis but may perpetuate the trouble. The use of a raised bite is of course only temporary. If the click is a cartilaginous one the same dental measures can be adopted, but in some instances a good result may follow surgical removal of the cartilage—an operation which is not as easy of performance as it may sound and which involves a definite risk of damage to the uppermost fibres of the facial nerve.

Desensitization to Foods

Q.—Could you let me know (in view of letters that have recently appeared in the JOURNAL on desensitizing patients suffering from pernicious anaemia, to extracts of liver): (1) Whether it is possible to desensitize patients suffering from allergy to other food proteins by injection of extracts of such foods, and if not, why it should be possible only to desensitize against liver extracts and not other foods? (2) Whether it is possible to desensitize them by other means. (3) What is the method employed in the procedure? (4) If it is possible to desensitize them, why do the textbooks all say it is not possible to desensitize them? (5) Why do allergic specialists also say it is impossible? (6) If it is possible to desensitize them, do they remain desensitized for life? If not, how long does the effect last? (7) Can desensitization do any harm? After undergoing a course, may the patient become more sensitive in future to the substance than he was before?

A.—(1) There is some confusion of thought here. The patients with pernicious anaemia under discussion were sensitive to the injection of liver extract but not to the ingestion of whole liver by mouth. Their symptoms were not those of food allergy. Analogous is the fact that such people as bakers, who get asthma from the inhalation of dust containing wheat flour, may be successfully desensitized by injection of wheat extracts, whereas a similar procedure is usually disappointing in patients who are sensitive to wheat foods taken by mouth. Why it is so rarely possible to desensitize patients to foods by hypodermic injection is not known, but it may depend on the disparity between the dose which can be given by injection and the amount which is normally taken by mouth. In any event, desensitization to foods by the parenteral injection of extracts is only rarely successful.

(2), (3), (4), (5). Oral desensitization, in which increasing doses of the food or an extract of it are given by mouth, is perhaps a little more successful than hypodermic desensitization, but it does not often succeed.

(6) Children often pass through a phase of sensitivity to a particular food and then grow out of it, but in the rare cases where active desensitization to food is successful in the adult, one would certainly not expect it to last for life. Sensitivity might well return within a month of omitting treatment. A more passive type of desensitization occurs when the offending food is eliminated from the diet for some weeks or months. In these circumstances patients may have no symptoms the first time they ingest the food again, but will probably have them if ingestion is repeated in 24 or 48 hours.

(7) There is no evidence that desensitization can do any harm, apart from the accidents of desensitization itself. On the contrary, experience with pollen therapy, which is the best known of all forms of desensitization, suggests that desensitization tends to produce some permanent lowering in sensitivity.

Phenobarbitone Poisoning

Q.—What is the treatment of acute phenobarbitone poisoning? Picrotoxin is usually advised, but I have never been able to find the correct dosage.

A.—Picrotoxin is probably superior to most of the antidotes to barbiturate poisoning, but it is more toxic. Large doses are tolerated in phenobarbitone poisoning. Thus, whereas the *B.P.C.* maximum dose is 1/25 gr., in barbiturate poisoning it is recommended to give doses of 1/6 gr. intramuscularly half-hourly until muscular twitching occurs. Intravenous nikethamide is usually very efficacious and far less dangerous.

Local Anaesthesia and Dental Extraction

Q.—Is there any contraindication, and if so what, to the administration of a local anaesthetic—e.g., novocain—in dental extractions? Is prolonged nerve irritation ever likely to supervene?

A.—A local anaesthetic for the extraction of a tooth should not be given when there is an acute abscess, and it is unwise to inject into or through an inflamed area. When the outer plate of alveolus is dense it may be impossible to obtain a satisfactory anaesthesia by a local infiltration, especially in the lower jaw. In these cases a regional injection is better. Many patients have a definite dislike of any form of local anaesthesia and may feel faint and ill after the injection. Some seem to be hypersensitive to the adrenaline which is contained in most of the solutions. Local anaesthesia should not be used with patients who are in a low state of health. Arterio-

sclerosis and organic heart disease are also contraindications. Prolonged nerve irritation when it occurs is more likely to be due to trauma or sepsis than to the injection.

Endocrine Types and Measurements

Q.—*Certain anthropomorphic measurements—e.g., span, vertex to pubis, pubis to heel, total height, circumference of head, chest, etc.—have been described by endocrinologists for the differentiation of endocrine types. Are these measurements, and the types which are distinguished from them, of recognized significance?*

A.—The exact significance of the endocrine types is not yet generally recognized, though most authorities would agree that they have significance. The subject is one for research, and not for dogmatic statement. The same or similar measurements are also used for distinguishing quantitatively the races of mankind—white, black, yellow, etc.—and subdivisions—Alpine, Mediterranean, Nordic, etc.—and even in the major racial subdivisions there are overlappings. Attempts have also been made, notably by Kretschmer and more recently by Sheldon, to use similar measurements to distinguish temperamental types. Here also the whole subject is fluid. All the work on endocrine types is on rather a small scale, and much further work is required, though it is pretty certain that valuable data will be derived in the end. At present we have certain knowledge only in the case of the frankly pathological—e.g., Fröhlich's syndrome.

The Diseases named "Pick"

Q.—*What is Pick's disease? And what is polyserositis, and what are its signs and symptoms? Pick's disease is described in Beaumont's "Medicine" (1939) as "a diffuse proliferative peritonitis often associated with similar proliferative changes in the mediastinum, pericardium, and pleura." In Beattie and Dickson's "Pathology" (1943) Pick's disease is "a comparatively circumscribed progressive degeneration and atrophy affecting the cortical nerve cells of the brain."*

A.—The use of eponyms is much to be deplored. They are responsible for great confusion and they tend to perpetuate outmoded conceptions. At least four men named Pick have had diseases called after them. Arnold Pick gave his name to a form of circumscribed atrophy of the brain, characterized by dementia, progressive degeneration of the higher faculties, and the development of aphasia. Alzheimer's disease and Arnold Pick's disease are two distinct subgroups of the condition known as pre-senile psychosis or sclerosis. The *Standard Nomenclature of Disease* unfortunately omits this form of Pick's disease in its list of eponyms, and the correct designation of the condition would presumably be "pre-senile sclerosis (Pick)."

Filipp Josef Pick gave his name to erythromelia, the initial stage of progressive idiopathic atrophy of the skin.

Ludwig Pick gave his name to the Pick's cell in Niemann-Pick disease, which the *Standard Nomenclature* calls "xanthomatosis (Niemann-Pick)," and which English writers would prefer to call "lipoid reticulosis (cholesterol)."

Friedel Pick gave his name to polyserositis and more particularly to the syndrome now known as constrictive pericarditis—recurrent ascites, enlargement of the liver, and oedema of the lower extremities, with a heart of normal size and without orthopnoea. It is believed that in these cases the ascites is mechanical in origin; the heart is unable to expand and fill with blood in diastole and the venous pressure therefore rises. When proliferative changes occur in the pleura and peritoneum in association with adhesive pericarditis the term Concato's disease is sometimes used; this syndrome is very rare. It is impossible to draw hard-and-fast distinctions, as all the different varieties of chronic pericarditis and polyserositis are usually tuberculous in origin. It is, however, vitally important to pick out cases of constrictive pericarditis, in which the constriction of the heart is preventing diastolic filling, as the patient can be strikingly relieved by surgical operation.

Asymmetry of Labia

Q.—*A girl aged 19 years is worried about her left labium being larger than the right since the age of 12 years. Examination findings confirm the patient's observations, but there is no other abnormality. What treatment or advice should be given?*

A.—Unequal development of bilateral organs is common, and, so far as the vulva is concerned, the asymmetry is mostly seen in connexion with the labia minora. It is presumed that such is the case here, and that the labia majora are not involved. Unilateral hypertrophy, unlike bilateral hypertrophy, of the nymphae is not likely to be caused by masturbation, and is to be regarded as a developmental anomaly. Any difference in size, if present, would hardly be noticed before puberty, since until that time the labia are undeveloped. This condition is not rare and has no special clinical significance. The patient should be reassured accordingly. No treatment is indicated unless the labium is so prominent as to get chafed by the thighs: in that case partial or total removal may be required.

Oral Vaccines for "Colds"

Q.—*Would you give me an authoritative opinion on the value of oral vaccines, with special reference to their use in the prevention of "colds and bronchitis"?*

A.—There are two formidable objections in theory to regarding this proceeding as even possibly beneficial. One applies to cold vaccines however administered: it is simply that they do not contain the causative organism, which is a filterable virus. Granting that some colds are due to bacterial infection, or that virus colds are increased in severity or prolonged by secondary bacterial infection, then the ordinary type of cold vaccine has some semblance of applicability; but so many species are concerned, some of which include many distinct antigenic types, that such a vaccine cannot contain every organism likely to be encountered, and the more it does contain the less, presumably, will be the degree of immunity produced to each. The second difficulty is in accepting the idea that a vaccine administered by the alimentary tract is going to immunize the respiratory tract. This is going further than Besredka, who introduced oral vaccine for enteric fever on the assumption that the tissue involved in the disease itself could be locally immunized. The efficiency even of this proceeding is by no means generally accepted, but it is asking much more of a swallowed vaccine that it shall enhance the resistance of another tissue altogether.

The theoretical improbabilities involved are therefore extreme, but perhaps we do not know enough about immunity to catarrhal infections to condemn such a proceeding out of hand. There is some clinical evidence which, so far as it goes, appears to be favourable to the method: G. E. Rockwell *et al.* (*J. Lab. clin. Med.*, 1937, **22**, 912) claim to have reduced the incidence of colds greatly, as compared with untreated controls, by frequently repeated oral doses of a dried preparation containing many billions of four species of bacteria. The dosage employed by these authors was greater than that afforded by some commercially available preparations.

LETTERS, NOTES, ETC.

Wasp and Bee Stings

Dr. O. H. BROWN (Guildford) writes: In the "Any Questions?" section of Aug. 26 (p. 295) there was a reply under the above heading. On Aug. 20, 1919, the *Times* published a letter from Edward R. Speyer, M.A.(Oxon), F.E.S. Since reading that letter I have never had a moment's anxiety in dealing with wasp stings. There was an interesting correspondence on the same subject 19 years later to which I contributed two letters (published in the *Times* of Aug. 23, 1938, and Aug. 30, 1938). The *Lancet* (Oct. 11, 1941) also has a letter of mine on the subject. The gist of the matter may be summed up in the mnemonic—"A.B., V.W.": alkalis for bee stings, vinegar for wasp stings.

Tug-of-war for Girls

Dr. K. A. GRANT (Corsham, Wilts) writes: I read with interest your answer under the above heading in the *Journal* of Aug. 12 (p. 230). When in labour, a girl or woman is forced to undergo "comparatively long periods of stasis with contracted muscles and fixed thorax," so what harm will a tug-of-war, which lasts only a short time, do?

Wooden Bullets

Major H. B. C. POLLARD writes: The German "wooden bullet" so painstakingly radiographed by Dr. Norman P. Henderson (*B.M.J.*, Sept. 9, p. 356) is incapable of producing injury at five yards, let alone 100! These are simply wooden "bulleted blanks" used in machine-guns where back gas pressure is needed to function the mechanism. They are in use in most Continental armies, and recent experiment at Woolwich Arsenal has shown that all German and Italian wooden bullets break up at the muzzle of a rifle and will not penetrate a cardboard screen at six feet. The whole business of wooden bullets is a soldier's story, but it is quite true that "the scattered fragments are not likely to be localized by radiological methods."

War Damage Contributions

H. S. owns a house which is mortgaged to a building society. It is used partly for professional purposes but "primarily as a private residence." Is he liable to the whole or only to a part of the war damage contribution?

⁂ The whole—and this would be the case if the property was used entirely for residential purposes. (The building society may be liable to recoup H. S. for part of his payment; whether and to what extent depends on the origin and relative amount of the mortgage.)

Correction

The third journal cited in footnote 3 to the leading article on problems of ariboflavinosis (July 29, p. 153) referring to the work of Fitzgerald Moore should read: *J. trop. Med. Hyg.*, 1939, **42**, 109.